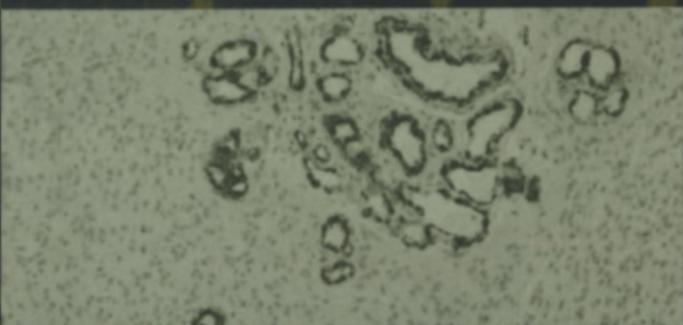


Davide  
Schiffer

# Brain Tumors

Biology,  
Pathology,  
and Clinical  
References

Second  
Revised Edition



**Ansichts-  
exemplar**



Springer

---

## Davide Schiffer · Brain Tumors



---

# Springer

*Berlin*

*Heidelberg*

*New York*

*Barcelona*

*Budapest*

*Hong Kong*

*London*

*Milan*

*Paris*

*Santa Clara*

*Singapore*

*Tokyo*

---

Davide Schiffer

# Brain Tumors

Biology, Pathology, and Clinical References

Second Revised Edition

With the Collaboration of Maria Teresa Giordana  
Alessandro Mauro · Riccardo Soffietti

With 286 Figures in 459 Separate Illustrations



Springer

---

Professor Dr. Davide Schiffer  
Professor Dr. Maria Teresa Giordana  
Dr. Alessandro Mauro  
Dr. Riccardo Soffietti

Department of Neurology, University of Turin  
Via Cherasco 15, 10126 Turin, Italy

ISBN 3-540-61622-5 2. Auflage  
Springer-Verlag Berlin Heidelberg New York

ISBN 3-540-55864-0 1. Auflage  
Springer-Verlag Berlin Heidelberg New York  
ISBN 0-387-55864-0 1st Edition  
Springer-Verlag New York Berlin Heidelberg

Library of Congress Cataloging-in-Publication Data  
Schiffer, Davide.

Brain tumors: biology, pathology, and clinical references/Davide Schiffer, with the collaboration of Maria Teresa Giordana, Alessandro Mauro, Riccardo Soffietti. – 2nd rev. ed. p. cm. Includes bibliographical references and index.

ISBN-13: 978-3-642-64445-0 e-ISBN-13: 978-3-642-60529-1  
DOI: 10.1007/978-3-642-60529-1

1. Brain-Tumors-Pathophysiology. 2. Brain-Tumors-Histopathology. I. Title. [DNLM: 1. Brain Neoplasms-pathology. WL 358 S333b 1997]  
RC280.B7S339 1997 616.99'281-dc20 DNLMDLC 96-41506

This work is subject to copyright. All rights are reserved, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilm or in any other way, and storage in data banks. Duplication of this publication or parts thereof is permitted only under the provisions of the German Copyright Law of September 9, 1965, in its current version, and permission for use must always be obtained from Springer-Verlag. Violations are liable for prosecution under the German Copyright Law.

© Springer-Verlag Berlin Heidelberg 1993, 1997  
Softcover reprint of the hardcover 1st edition 1997

The use of general descriptive names, registered names, trademarks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

Product liability: The publishers cannot guarantee the accuracy of any information about the application of operative techniques and medications contained in this book. In every individual case the user must check such information by consulting the relevant literature.

Typesetting: Elsner & Behrens, Ostersheim  
Printing: Saladruck, Berlin  
Binding: Lüderitz & Bauer, Berlin

SPIN: 1050 7800 25/3135 - 5 4 3 2 1 0

---

## Preface to the Second Edition

Neurooncology has become a science of such great proportions and indefinite limits as to include branches which widely diverge from one another. Therefore, it is not an easy task to fit it all into the narrow framework of a book, though the collaboration among scientists compensates partly for the varying depths of knowledge and experience in the individual disciplines. The principal characteristic of this work, however, is in casting “pathology” as the common nosographic link.

Though scientific progress has brought us well past the nosography of brain tumors, pathology remains the point of departure, the area of mutual understanding to which all students of neurooncology refer when laying out diagnostic, therapeutic, and research schedules. Neurologists, neurosurgeons, and neuroradiologists orient themselves only by referring to tumor types.

Neurooncology treatises require ever greater numbers of authors in order to cover the different subject areas with uniform authority. Excellent texts are available today for this purpose. The present book is not, and does not wish to be, a treatise but rather aims at presenting different aspects of neurooncology from the perspective of pathology and its biological and clinical correlates. It expresses the author's experience in the study of brain tumors and their pathology and clinical characteristics. The emphasis dedicated to the subjects relates to the clinicopathological and theoretical importance.

The characteristics of the first edition as described above have been preserved; the clinical applications have been amplified and the biological and pathological problems updated. The unity of perspectives, as mentioned, has been favored over delving into the details of particular areas.

The book is the product of the clinical and pathological experience gained at a single institution, and in this endeavor it conforms to some great books on brain tumors of the past. This may be anachronistic, but has the advantage of uniformity.

As to the references, in comparison with the first edition, many items have been omitted and new items have, obviously, been inserted. At first glance, they appear to be too numerous but this is a wrong impression considering the number of scientific contributions which have appeared in the main scientific journals in the past years. Evenso, the list of references is not exhaustive, so that important contributions may not have been included.

The book is addressed to pathologists, neuropathologists, neurosurgeons, neurologists and to all those working in the field of neurooncology who deal for one reason or another with pathology and its application in clinical practice.

Many thanks to all those who directly or indirectly collaborated in this work, and, in particular, Dr. Antonio Migheli, Dr. Maria Claudia Vigliani, Dr. Paola Cavalla, and

Mrs. Annalisa Ferraiolo for histological preparations. The warmest thanks to Professor Anthony Raimondi for his support and constant encouragement.

Turino, September 1996

Davide Schiffer

---

## Preface to the First Edition

Neuro-oncology has in the past decade undergone tremendous developments, so much so that it is now a scientific field of vast proportions. Molecular and genetic biology, on the one hand, and the improvements in imaging techniques, therapies, and general management, on the other, have been highly instrumental in effecting this progress. Despite all recent developments, descriptive pathology, however, with its many biological correlates – foremost among them immunohistochemistry – and, therefore, histological diagnosis and prognostic assessment continue to be the reference points for judging all new achievements in neuro-oncology.

Years of experience of patients with brain tumors and collaboration with neurosurgeons, neuro-oncologists, neuro-radiologists, radiotherapists, and neurobiologists have taught us that the pathologist supplying the histological diagnosis may in fact sometimes fail to get across the biological message. Sometimes this failure arises because it is really impossible for pathology to provide the expected nosographic definition of a tumor. Sometimes, by contrast, it is due to real difficulties in understanding the language of the pathologist. This is particularly true when the prognosis deducible from the diagnostic label is not unequivocal. In attempting to be objective, the pathologist counterbalance the lack of a clear-cut definition with a detailed histological description, which means that everything depends upon his partners' ability to interpret this information properly.

The aim of this book is thus to provide neurologists, neurosurgeons, neuro-oncologists and interested students of this subject with a broad knowledge base on the pathology of brain tumors.

The book describes the pathology of brain tumors and its relationship to clinical and biological features, taking particular account of the importance of the various problems from a general neuro-oncological point of view. Such a treatment may risk giving the impression that disproportionate attention is given to some topics, at the expense of others. However, the aim of the book was to describe and discuss the various subjects in the light of their clinical and biological importance during this historic period of development. Accordingly, the initial chapters on ontogenesis and immunohistochemistry must be considered of valuable help. Today, as everybody knows, some diagnoses are overused or even abused and some conditions are frequently overtreated. Such topics have also been given due attention in this book.

I am deeply indebted to many colleagues who helped in preparing the volume: Dr. Humberto Cravioto New York University for supplying pictures; Dr. Antonio Migheli and Dr. Maria Claudia Vigliani of our Institute for their help in electron microscopy and immunohistochemistry, Mrs. Maria Teresa Bertello and Dr. Angelo Attanasio for their help in preparing the manuscript; and Mrs. Annalisa Ferraiolo for histological



preparations. I was helped with the English text by Dr. Marco L. Rossi, Charing Cross Hospital and Westminster Medical School, London, with the cooperation of Dr. Martin P. Carey, Queen Elizabeth II Hospital, Birmingham. Finally, my special thanks go to Dr. Anthony Raimondi for his scientific editing of the book.

Turino, Januar 1993

Davide Schiffer

---

# Contents

<b>1</b>	<b>Cytogenesis of the Central Nervous System . . . . .</b>	<b>1</b>
1.1	Neurogenesis and Gliogenesis . . . . .	1
1.2	Gliogenesis in Adult Animals . . . . .	8
1.3	Development of the Cerebellar Cortex . . . . .	10
1.4	Radial Glia and Ependyma . . . . .	11
1.5	Genes Controlling Nervous System Development . . . . .	15
<b>2</b>	<b>Factors of the Transformation Process . . . . .</b>	<b>18</b>
2.1	Genetics and Molecular Biology . . . . .	18
2.2	Familial Incidence of Tumors . . . . .	29
2.3	Congenital Tumors . . . . .	29
2.4	Risk Factors: Epidemiological Data . . . . .	30
2.4.1	Family Characteristics . . . . .	31
2.4.2	Individual Factors . . . . .	32
2.4.3	Multiple Sclerosis . . . . .	33
2.4.4	Virus . . . . .	33
2.4.5	Head Injuries . . . . .	33
2.4.6	Irradiation . . . . .	34
2.4.7	Nonprofessional Exogenous Exposures . . . . .	35
2.4.8	Professional Exogenous Exposures . . . . .	36
2.4.9	Multiple Tumors . . . . .	37
<b>3</b>	<b>Experimental Tumors . . . . .</b>	<b>39</b>
3.1	Chemical Carcinogenesis . . . . .	39
3.1.1	Topically Acting Carcinogens . . . . .	39
3.1.2	Resorptive Carcinogens . . . . .	39
3.1.2.1	Pathogenesis of Nitrosourea-Induced Tumors . . . . .	46
3.1.2.2	Cellular Composition . . . . .	48
3.1.2.3	Vascularization of ENU-Induced Tumors . . . . .	51
3.1.2.4	Utilization of MNU-ENU Models . . . . .	51

3.2	Viral Carcinogenesis . . . . .	52
3.3	Transplantable Animal Models . . . . .	53
3.4	Gene Transfer Models of Neural Tumors . . . . .	54
<b>4</b>	<b>Antigens of Phenotypic Expression and Differentiation Markers</b>	<b>56</b>
4.1	Brain Tumor-Associated Antigens . . . . .	56
4.2	Antigens Employed in the Histological Diagnosis of Brain Tumors . .	57
4.2.1	Glial Markers . . . . .	58
4.2.1.1	S-100 Protein . . . . .	58
4.2.1.2	Glial Fibrillary Acidic Protein . . . . .	60
4.2.1.3	Glutamine Synthetase . . . . .	61
4.2.1.4	Carbonic Anhydrase . . . . .	61
4.2.1.5	Myelin Basic Protein . . . . .	63
4.2.1.6	Myelin-Associated Glycoprotein . . . . .	63
4.2.2	Neuronal Markers . . . . .	64
4.2.2.1	Neuronal-Specific Enolase . . . . .	64
4.2.2.2	Neurofilaments . . . . .	64
4.2.2.3	Synaptophysin and Chromogranin . . . . .	65
4.2.3	Markers Nonspecific for the Nervous System . . . . .	65
4.2.4	Vessel Markers . . . . .	66
4.2.5	Other Intermediate Filaments . . . . .	68
4.2.6	Epithelial Membrane Antigens . . . . .	71
4.2.7	Markers for Cerebral Metastases . . . . .	71
<b>5</b>	<b>Pathology of the Host-Tumor Interaction . . . . .</b>	<b>74</b>
5.1	Peritumoral Changes . . . . .	74
5.1.1	Glial Reaction . . . . .	74
5.1.2	Included Neurons . . . . .	79
5.1.3	Ventricular Walls . . . . .	79
5.2	Regressive Events in the Tumor . . . . .	80
5.3	Cerebral Edema . . . . .	83
5.3.1	Definition and Pathogenesis . . . . .	83
5.3.2	Morphological Changes and Sequelae . . . . .	86
5.4	Calcifications . . . . .	89
5.5	Immune Response . . . . .	92
<b>6</b>	<b>Classification and Nosography of Neuroepithelial Tumors . . . . .</b>	<b>96</b>

<b>7</b>	<b>The Concept of Malignancy: Anaplasia, Cell Proliferation, Metastasis</b> . . . . .	<b>109</b>
7.1	General Considerations . . . . .	109
7.2	Cell Kinetics . . . . .	115
7.3	Metastasis . . . . .	122
7.4	Expansion and Invasiveness . . . . .	124
7.4.1	Invasion Mechanisms . . . . .	130
<b>8</b>	<b>Descriptive Epidemiology of Primary Nervous System Tumors</b> . .	<b>132</b>
8.1	General Data . . . . .	132
8.1.1	Mortality . . . . .	132
8.1.2	Incidence . . . . .	132
8.2	Epidemiology of Intracranial Tumors . . . . .	133
8.2.1	Histological Type . . . . .	134
8.2.2	Age . . . . .	134
8.2.3	Sex . . . . .	136
8.2.4	Race . . . . .	136
8.3	Epidemiology of Intraspinal Tumors . . . . .	136
<b>9</b>	<b>Astrocytic Tumors</b> . . . . .	<b>137</b>
9.1	Nosological Problems . . . . .	137
9.2	Astrocytic Tumors of the Cerebral Hemispheres . . . . .	139
9.2.1	Astrocytomas . . . . .	139
9.2.1.1	Frequency, Age, Site and Clinical Features . . . . .	139
9.2.1.2	Macroscopic Appearance and Imaging . . . . .	139
9.2.1.3	Microscopic Appearance . . . . .	139
9.2.1.4	Pilocytic Astrocytoma . . . . .	142
9.2.1.5	Anaplastic Variant . . . . .	147
9.2.1.6	Prognosis and Treatment of Hemispheric Astrocytomas . . . . .	150
9.2.2	Glioblastoma Multiforme . . . . .	155
9.2.2.1	General Considerations . . . . .	155
9.2.2.2	Frequency, Age, Site and Clinical Features . . . . .	156
9.2.2.3	Macroscopic Appearance and Imaging . . . . .	157
9.2.2.4	Microscopic Appearance . . . . .	159
9.2.2.5	Tumor Spreading . . . . .	169
9.2.2.6	Differential Diagnosis . . . . .	171
9.2.2.7	Giant Cell Variant . . . . .	171
9.2.2.8	Gliosarcoma . . . . .	172
9.2.2.9	Blood Vessel Architecture and Angiogenesis in Gliomas . . . . .	178

9.2.2.10	Cellular Kinetics . . . . .	185
9.2.2.11	Metabolism . . . . .	185
9.2.2.12	Prognosis and Treatment . . . . .	187
9.2.3	Gliomatosis Cerebri . . . . .	189
9.2.4	Pleomorphic Xanthoastrocytoma . . . . .	190
9.2.4.1	Macroscopic Appearance . . . . .	190
9.2.4.2	Microscopic Appearance . . . . .	191
9.2.4.3	Prognosis . . . . .	193
9.2.5	Subependymal Giant Cell Astrocytoma (Tuberous Sclerosis) . . . . .	193
9.2.6	Astroblastoma . . . . .	196
9.3	Astrocytic Tumors of the Midline . . . . .	197
9.3.1	Astrocytoma of the Optic Nerve . . . . .	198
9.3.2	Astrocytoma of the Chiasm . . . . .	199
9.3.3	Brain Stem Astrocytomas . . . . .	201
9.3.4	Other Midline Astrocytomas . . . . .	203
9.3.5	Cerebellar Astrocytomas . . . . .	203
9.3.5.1	Nosographic Considerations . . . . .	203
9.3.5.2	Frequency, Age . . . . .	204
9.3.5.3	Macroscopic Appearance . . . . .	204
9.3.5.4	Microscopic Appearance . . . . .	204
9.3.5.5	Rosenthal's Fibers . . . . .	209
9.3.5.6	Malignant Transformation, Prognosis . . . . .	210
9.4	Astrocytic Tumors of the Spinal Cord . . . . .	213
9.4.1	Frequency, Age . . . . .	213
9.4.2	Macroscopic and Microscopic Appearance . . . . .	213
<b>10</b>	<b>Oligodendroglial Tumors . . . . .</b>	<b>214</b>
10.1	Oligodendroglioma . . . . .	214
10.1.1	Frequency, Age, Site and Clinical Features . . . . .	214
10.1.2	Macroscopic Appearance and Imaging . . . . .	214
10.1.3	Microscopic Appearance . . . . .	216
10.2	Presence of Astrocytes and the Problem of Mixed Gliomas: Oligoastrocytoma . . . . .	221
10.3	Anaplastic Oligodendroglioma and Prognosis . . . . .	223
<b>11</b>	<b>Ependymal Tumors . . . . .</b>	<b>228</b>
11.1	Ependymoma . . . . .	228
11.1.1	Classification Problems . . . . .	228
11.1.2	Frequency, Age, Sex, Site and Clinical Features . . . . .	230
11.1.3	Macroscopic Appearance and Imaging . . . . .	231
11.1.4	Microscopic Appearance . . . . .	233

11.1.5	Regressive Events . . . . .	237
11.1.6	Immunohistochemistry . . . . .	239
11.1.7	Electron Microscopy . . . . .	242
11.1.8	Anaplastic Ependymoma . . . . .	245
11.1.9	Spread Via the Cerebrospinal Fluid . . . . .	248
11.1.10	Treatment and Prognosis . . . . .	248
11.2	Subependymoma . . . . .	249
11.3	Ependymoblastoma . . . . .	252
<b>12</b>	<b>Choroid Plexus Tumors . . . . .</b>	<b>254</b>
12.1	Plexus-Papilloma . . . . .	254
12.1.1	Frequency, Age, Site and Clinical Features . . . . .	254
12.1.2	Macroscopic Appearance and Imaging . . . . .	255
12.1.3	Microscopic Appearance . . . . .	256
12.1.4	Treatment and Prognosis . . . . .	256
12.2	Malignant Variant (Plexus Carcinoma) . . . . .	259
<b>13</b>	<b>Tumors Composed of Neural Cells . . . . .</b>	<b>260</b>
13.1	Ganglioglioma (Gangliocytoma) . . . . .	260
13.1.1	Frequency, Age, Site and Clinical Features . . . . .	260
13.1.2	Macroscopic Appearance and Imaging . . . . .	261
13.1.3	Microscopic Appearance . . . . .	262
13.1.4	Malignant Transformation (Malignant Ganglioglioma) . . . . .	264
13.1.5	Prognosis . . . . .	266
13.2	Dysplastic Gangliocytoma of the Cerebellum . . . . .	266
13.3	Infantile Desmoplastic Ganglioglioma – Desmoplastic Infantile Astrocytoma . . . . .	267
13.4	Central Neurocytoma . . . . .	268
13.5	Dysembryoplastic Neuroepithelial Tumors . . . . .	270
13.6	Olfactory Neuroblastoma . . . . .	272
<b>14</b>	<b>Pineal Gland Tumors . . . . .</b>	<b>275</b>
14.1	The Pineal Gland . . . . .	275
14.2	Pineal Gland Tumors . . . . .	276
14.2.1	Pineocytoma . . . . .	277
14.2.1.1	Macroscopic Appearance . . . . .	277
14.2.1.2	Microscopic Appearance . . . . .	277
14.2.1.3	Treatment and Prognosis . . . . .	281
14.2.2	Pinealoblastoma . . . . .	281



14.2.2.1	Macroscopic Appearance . . . . .	281
14.2.2.2	Microscopic Appearance . . . . .	282
14.2.2.3	Prognosis . . . . .	285
14.2.4	Trilateral Retinoblastoma . . . . .	285
14.3	Pineal Cysts . . . . .	285
<b>15</b>	<b>Embryonal Tumors . . . . .</b>	<b>287</b>
15.1	Medulloepithelioma . . . . .	287
15.2	Medulloblastoma . . . . .	289
15.2.1	Frequency, Age and Clinical Features . . . . .	289
15.2.2	Macroscopic Appearance and Imaging . . . . .	289
15.2.3	Microscopic Appearance . . . . .	291
15.2.3.1	Desmoplastic Variant . . . . .	297
15.2.3.2	Melanotic Medulloblastoma . . . . .	298
15.2.3.3	Medullomyoblastoma . . . . .	298
15.2.4	DNA Content and Pathology . . . . .	299
15.2.5	Problem of Differentiation . . . . .	299
15.2.6	Prognosis, Recurrence, Metastasis . . . . .	305
15.2.7	Medulloblastoma of Adults . . . . .	307
15.3	Neuroblastoma . . . . .	308
15.3.1	Macroscopic Appearance . . . . .	308
15.3.2	Microscopic Appearance . . . . .	308
15.3.3	Prognosis . . . . .	311
15.4	Polar Spongioblastoma . . . . .	311
15.5	Appendix: Tumors of the Retina . . . . .	313
15.5.1	Retinoblastoma . . . . .	315
<b>16</b>	<b>Glomus Tumors, Paragangliomas . . . . .</b>	<b>319</b>
16.1	Site, Age, and Clinical Features . . . . .	319
16.2	Macroscopic Appearance and Imaging . . . . .	320
16.3	Microscopic Appearance . . . . .	321
16.4	Prognosis . . . . .	321
<b>17</b>	<b>Tumors of the Cranial and Spinal Nerves . . . . .</b>	<b>322</b>
17.1	Neurinoma (Schwannoma) . . . . .	322
17.1.1	Frequency, Age, Sex . . . . .	322
17.1.2	Site . . . . .	323
17.1.3	Clinical Features . . . . .	325

17.1.4	Macroscopic Appearance and Imaging . . . . .	326
17.1.5	Microscopic Appearance . . . . .	327
17.1.6	Cellular Schwannoma . . . . .	333
17.1.7	In Vitro Culture . . . . .	333
17.2	Neurofibromas . . . . .	334
17.2.1	Plexiform Neurofibromas . . . . .	335
17.3	Granular Cell Tumors . . . . .	335
17.4	Neurothekeoma . . . . .	336
17.5	Perineurioma . . . . .	336
17.6	Prognosis, Malignancy . . . . .	336
<b>18</b>	<b>Tumors of the Meninges . . . . .</b>	<b>341</b>
18.1	Meningiomas . . . . .	341
18.1.1	General Considerations and Nomenclature . . . . .	341
18.1.2	Frequency . . . . .	343
18.1.3	Age . . . . .	343
18.1.4	Sex . . . . .	344
18.1.5	Familial Tendency . . . . .	344
18.1.6	Trauma and Irradiation . . . . .	344
18.1.7	Association with Other Tumors . . . . .	345
18.1.8	Site . . . . .	346
18.1.9	Multiple Meningiomas . . . . .	349
18.1.10	Clinical Features and Imaging . . . . .	349
18.1.11	Macroscopic Appearance . . . . .	352
18.1.12	Microscopic Appearance . . . . .	353
18.1.12.1	Angiomatous Meningiomas . . . . .	356
18.1.12.2	Malignant Meningioma . . . . .	359
18.1.13	Metaplasia in Meningiomas . . . . .	362
18.1.14	Regressive Changes . . . . .	367
18.1.15	Calcifications . . . . .	369
18.1.16	Electron Microscopy . . . . .	374
18.1.17	Receptors for Steroid Hormones . . . . .	375
18.1.18	In Vitro Culture . . . . .	376
18.1.19	Growth Modality . . . . .	377
18.1.20	Metastasis . . . . .	380
18.1.21	Prognosis, Treatment . . . . .	380
18.2	Other Mesenchymal Tumors of the Meninges . . . . .	382
18.2.1	Benign Neoplasms . . . . .	382
18.2.2	Malignant Neoplasms . . . . .	383
18.2.2.1	Hemangiopericytoma . . . . .	383
18.2.2.2	Fibrosarcoma . . . . .	386
18.2.2.3	Malignant Fibrous Histiocytoma . . . . .	386
18.2.2.4	Primary Meningeal Sarcomatosis . . . . .	388

18.2.2.5	Primitive Melanoblastosis of the Leptomeninges . . . . .	388
18.2.2.6	Primary Melanotic Lesions . . . . .	390
18.2.2.7	Meningiomatosis or Meningoangiomatosis . . . . .	391
18.2.2.8	Miscellaneous . . . . .	391
<b>19</b>	<b>Mesenchymal Tumors . . . . .</b>	<b>392</b>
19.1	Chordomas . . . . .	392
19.1.1	General Considerations . . . . .	392
19.1.2	Macroscopic Appearance . . . . .	393
19.1.3	Microscopic Appearance . . . . .	395
19.1.4	Electron Microscopy . . . . .	396
19.1.5	Differential Diagnosis . . . . .	396
19.1.6	Prognosis . . . . .	397
19.2	Chondroma . . . . .	397
19.3	Chondrosarcomas . . . . .	398
19.4	Osteomas . . . . .	400
19.5	Osteosarcoma . . . . .	401
<b>20</b>	<b>Vascular Tumors . . . . .</b>	<b>402</b>
20.1	Capillary Hemangioblastoma . . . . .	402
20.1.1	Biological Data . . . . .	402
20.1.2	Macroscopic Appearance . . . . .	403
20.1.3	Microscopic Appearance . . . . .	404
20.1.4	Regressive Events . . . . .	409
20.1.5	Electron Microscopy Study . . . . .	410
20.1.6	Metastasis, Recurrences, Prognosis . . . . .	410
20.1.7	Associated Polycythemia . . . . .	411
20.1.8	Differential Diagnosis . . . . .	411
<b>21</b>	<b>Tumors and Dysontogenetic Lesions . . . . .</b>	<b>412</b>
21.1	Germ Cell Tumors . . . . .	412
21.1.1	Frequency, Age, Sites, Clinical Features, Imaging . . . . .	412
21.1.2	Pathogenesis . . . . .	414
21.1.3	Germinoma . . . . .	414
21.1.3.1	Macroscopic Appearance . . . . .	414
21.1.3.2	Microscopic Appearance . . . . .	414
21.1.3.3	Prognosis, Treatment . . . . .	416
21.1.4	Embryonal Carcinoma . . . . .	417
21.1.5	Choriocarcinoma . . . . .	417
21.1.6	Endodermal Sinus Tumor . . . . .	417

21.1.7	Teratocarcinoma . . . . .	419
21.1.8	Immunohistochemical and Chemical Characterization . . . . .	419
21.2	Teratomas . . . . .	419
21.2.1	Frequency, Age, Site . . . . .	420
21.2.2	Macroscopic Appearance . . . . .	420
21.2.3	Microscopic Appearance . . . . .	421
21.2.4	Prognosis, Recurrence . . . . .	421
21.3	Tumors with Muscle Cells . . . . .	424
21.3.1	Medullomyoblastoma . . . . .	424
21.3.2	Primitive CNS Rhabdomyosarcoma . . . . .	427
21.3.3	Other Tumors . . . . .	429
21.3.4	Rhabdoid Tumors . . . . .	429
21.4	Dermo-epidermoid Cysts . . . . .	430
21.4.1	Nosography, Pathogenesis . . . . .	430
21.4.2	Frequency, Age, Site and Clinical Features . . . . .	430
21.4.3	Macroscopic Appearance and Imaging . . . . .	431
21.4.4	Microscopic Appearance . . . . .	433
21.4.5	Prognosis, Sequelae . . . . .	435
21.5	Craniopharyngioma and Epithelial Cysts . . . . .	435
21.5.1	Embryogenetic Aspects . . . . .	435
21.5.2	Incidence . . . . .	437
21.5.3	Site . . . . .	438
21.5.3.1	Intraventricular Tumors . . . . .	439
21.5.4	Clinical Aspects . . . . .	439
21.5.5	Macroscopic Appearance . . . . .	440
21.5.6	Microscopic Appearance . . . . .	443
21.5.6.1	Electron Microscopy and Immunohistochemistry . . . . .	447
21.5.6.2	Calcification . . . . .	450
21.5.6.3	Cystic Component . . . . .	451
21.5.7	Adjacent Tissue . . . . .	454
21.5.8	Relationships of Craniopharyngiomas with Rathke's Fissure Cysts . . . . .	454
21.5.9	Prognosis, Treatment . . . . .	458
21.6	Neuroepithelial and Non-Neuroepithelial Cysts . . . . .	459
21.6.1	Colloid Cysts of the Third Ventricle . . . . .	459
21.6.1.1	Frequency, Age, Site . . . . .	460
21.6.1.2	Macroscopic Appearance . . . . .	460
21.6.1.3	Microscopic Appearance . . . . .	460
21.6.2	Spinal Enterogenous Cysts . . . . .	462
21.6.3	Arachnoid Cysts . . . . .	462
21.7	Lipomas . . . . .	462
21.7.1	Frequency, Age, Site . . . . .	463
21.7.2	Macroscopic Appearance . . . . .	464
21.7.3	Microscopic Appearance . . . . .	464
21.7.4	Prognosis, Treatment . . . . .	464

21.8	Hamartomas, Ectopias, and Ectopic Tumors . . . . .	465
21.8.1	Hamartoma of the Hypothalamus . . . . .	465
21.8.2	Granule Cell Tumors . . . . .	465
21.8.3	Meningeal Gliomas . . . . .	467
21.8.4	Ectopic Gliomas and Neural Hamartomas . . . . .	468
21.9	Hamartomas or Vascular Malformations . . . . .	468
21.9.1	Clinical Features . . . . .	469
21.9.2	Capillary Teleangectasias . . . . .	469
21.9.3	Cavernous Angioma . . . . .	470
21.9.4	Arteriovenous Malformation . . . . .	472
21.9.4.1	Dural Arteriovenous Malformations . . . . .	473
21.9.5	Venous Malformations . . . . .	473
<b>22</b>	<b>Phakomatosis and Dysgenetic Syndromes . . . . .</b>	<b>475</b>
22.1	Tuberous Sclerosis (Bourneville's Disease) . . . . .	475
22.2	Neurofibromatosis . . . . .	477
22.2.1	Neurofibromatosis-1 or von Recklinghausen's Disease . . . . .	479
22.2.1.1	Clinical Course . . . . .	480
22.2.2	Neurofibromatosis-2 . . . . .	480
22.2.3	Associated Lesions of a Dysplastic Nature . . . . .	481
22.3	Von Hippel-Lindau Syndrome . . . . .	481
22.4	Sturge-Weber Syndrome . . . . .	482
22.5	Other Dysgenetic Syndromes . . . . .	483
<b>23</b>	<b>Primary Central Nervous System Lymphomas . . . . .</b>	<b>484</b>
23.1	Frequency, Age, Site, and Clinical Features . . . . .	486
23.2	Macroscopic Aspect and Imaging . . . . .	486
23.3	Microscopic Appearance . . . . .	487
23.4	Epidural Lymphomas . . . . .	496
23.5	Lymphomas in AIDS . . . . .	496
23.6	Prognosis, Treatment . . . . .	496
<b>24</b>	<b>Metastases . . . . .</b>	<b>498</b>
24.1	Frequency . . . . .	498
24.2	Sex . . . . .	499
24.3	Age . . . . .	499
24.4	Metastatic Pathways . . . . .	499
24.5	Macroscopic Appearance and Imaging . . . . .	500
24.6	Microscopic Appearance . . . . .	502

24.7	Differential Diagnosis . . . . .	503
24.8	Prognosis and Therapy . . . . .	503
24.9	Carcinomatous Meningitis . . . . .	505
24.10	Spinal Metastases . . . . .	505
<b>25</b>	<b>Biological Basis of Therapies . . . . .</b>	<b>506</b>
25.1	Radiotherapy . . . . .	506
25.1.1	Cellular Response to Ionizing Radiation . . . . .	506
25.1.2	Therapeutic Studies with Low Linear Energy Transfer Radiation on Experimental Brain Tumors . . . . .	508
25.1.3	Methods of Improving the Therapeutic Ratio in Radiotherapy of Brain Tumors . . . . .	509
25.1.3.1	Altered Fractionation . . . . .	509
25.1.3.2	Brachytherapy . . . . .	509
25.1.3.3	Association with Chemotherapeutic Agents . . . . .	510
25.1.3.4	Radiosensitizers . . . . .	510
25.1.3.5	Hyperthermia . . . . .	511
25.1.3.6	Photoradiation Therapy . . . . .	512
25.1.3.7	High Linear Energy Transfer Radiation . . . . .	512
25.1.3.8	Radioprotectors . . . . .	512
25.2	Chemotherapy . . . . .	513
25.2.1	General Concepts . . . . .	513
25.2.2	Chemosensitivity and Chemoresistance in Brain Tumors . . . . .	513
25.2.3	Drug Delivery to Brain Tumors . . . . .	516
25.2.3.1	Intra-Cerebrospinal Fluid and Interstitial Chemotherapy . . . . .	517
25.2.3.2	Transient and Reversible Blood–Brain Barrier Modification . . . . .	518
25.2.3.3	Carrier Systems and Liposomes . . . . .	518
25.3	Immunotherapy . . . . .	519
25.4	Biologic Therapies . . . . .	520
<b>26</b>	<b>Effects of Treatment on Brain Tumors and Normal Nervous Tissue . . . . .</b>	<b>522</b>
26.1	Effects of Radiotherapy and/or Chemotherapy on Human Brain Tumors . . . . .	522
26.2	Effects of External Radiotherapy on the Human Brain . . . . .	523
26.3	Effects of Brachytherapy on the Human Brain . . . . .	531
26.4	Effects of External Radiotherapy on the Human Spinal Cord and/or Nerve Roots . . . . .	531
26.5	Pathogenesis of Adverse Effects of Radiotherapy on the Normal Nervous Tissue . . . . .	532
26.6	Effects of Chemotherapy on the Human Brain and Spinal Cord . . . . .	534



---

26.7	Effects of Treatment on Normal Nervous Tissue in Acute Lymphocytic Leukemia of Childhood . . . . .	534
26.8	Second Malignancies . . . . .	535
	<b>References . . . . .</b>	<b>536</b>
	<b>Subject Index . . . . .</b>	<b>689</b>

## Cytogenesis of the Central Nervous System

### 1.1

#### Neurogenesis and Gliogenesis

In man, during embryonal development, at the 18th day of intrauterine (i.u.) life, a thickening of the ectoderm (the neural placode) forms in the midline of the embryo. This thickening, induced by the notochord and by the parachordal mesoderm, subsequently infolds to form the neural groove. This latter closes on the 22nd day, giving rise to the neural tube. Before closure, the edges of the groove proliferate to form the neural crests from which cells of the dorsal roots and sympathetic ganglia, Schwann cells, melanocytes, and cells of the adrenal medulla originate.

The neural tube closes anteriorly at the level of the nasal-frontal groove (anterior neuropore) on the 28th–29th day of i.u. life and posteriorly at the L1–L2 level (posterior neuropore) on the 25th–27th day. Although still a matter of debate, the currently accepted view is that mesenchymal tissue, from which spinal meninges derive, interposes itself between the epiblast and the neural tube.

In the cephalic part, the neural tube is formed from three vesicles (caudal, intermediate, and rostral), respectively called rhombencephalic, mesencephalic, and prosencephalic. The neural tube gives origin to the spinal cord; the rhombencephalic vesicle to the medulla oblongata, pons, and cerebellum; the mesencephalic vesicle to mesencephalon; the prosencephalic vesicle to diencephalon and telencephalon. An early groove between the neural tube and the rhombencephalic vesicle, followed by ventral displacement of the encephalic anlage, gives rise to a cervical flexure which becomes the boundary between the spinal cord and encephalon. When the embryo is 11 mm in length, the rhombencephalic vesicle folds anteriorly, thereby forming a caudal and a cranial part. The former thickens ventrally, forming the myelencephalon from which the medulla oblongata develops. As the latter grows, it forms the metencephalon, from which the pons then develops. The dorsal part of the metencephalon undergoes a remarkable development and becomes the cerebellum.

When the embryo is 14 mm in length, the prosencephalic vesicle forms two symmetrical outpouchings anteriorly. These represent the anlagen of the cerebral hemispheres. The posterior part of the prosencephalon becomes diencephalon. The median structure which links the two pouches develops into the lamina terminalis. In the ventral part of the diencephalon, two symmetrical outpouchings develop, externalize, and thus give rise to the retinal anlage which remains bound to the diencephalon through peduncles, i.e., the optic nerves. The anlage of the hypophysis is formed in the midline of the diencephalon. Thus all the anlagen of the definitive segments of the central nervous system are present in the 15-mm embryo.

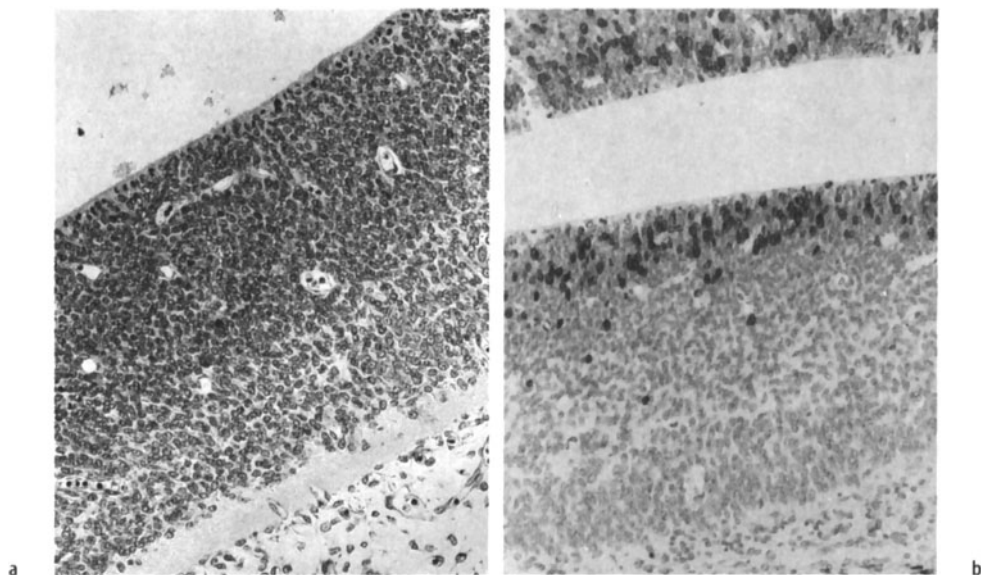


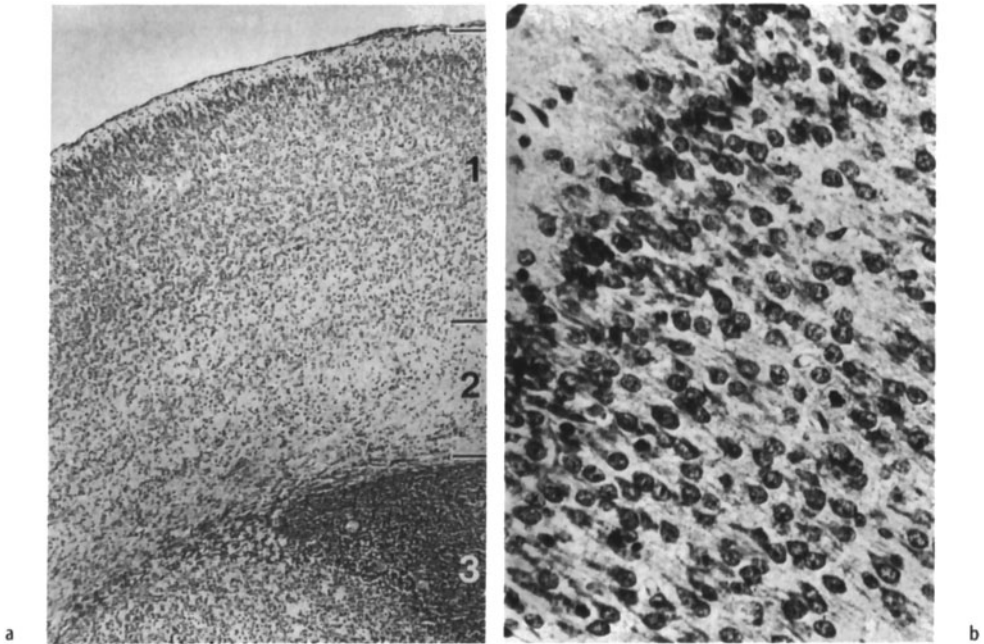
Fig. 1.1a,b. Rat embryo on day 14 of intrauterine life. Germinal layer. a H&E,  $\times 200$ . b Bromodeoxyuridine (BrdU) labeling. PAP-DAB,  $\times 200$

The fundamental parts of the central nervous system (CNS) are visible externally by the fourth month of gestation. The hypothalamus, mammillary bodies, tuber cinereum, and the hypophyseal peduncle develop from the ventral diencephalon; the two optic thalami originate from the dorsal part of the diencephalon. The telencephalon, which together with the diencephalon forms the prosencephalon, increases in volume and thus obscures the diencephalon. Its surface, initially smooth, becomes ever richer in folds, forming the sulci and gyri, including the anlage of the Sylvian fissure (which appears at the end of the third month of gestation).

The growth of the neural tube and of its derivatives is related to the existence of the ectodermal matrix, which is composed of stem cells capable of multiplication. The development consists initially of an increase in the number of matrix elements. Subsequently, as the differentiation process proceeds, the growth is mostly related to an increase in cell volume.

Most of our knowledge of the early phases of neural cytogenesis is based on studies carried out in rats [2787]. In the rat on the 12th day of i.u. life, the neuroepithelium of the telencephalon consists of pseudostratified epithelium, i.e., the ventricular zone.

In the ventricular zone, the stem cells multiply and subsequently migrate, giving rise to neurons and glial cells. In the first stages of development, the germinal cells of the neural tube are in asynchronous phases of the mitotic cycle, and all become labeled with  $[^3\text{H}]$ thymidine or bromodeoxyuridine (BrdU). The multiplication process of the germinal cells is characteristically accompanied by a mechanism of the to-and-fro movement of the nucleus. Nuclei in S phase are situated in the most external part of the layer while those in  $G_2$ -M phase are situated close to the lumen (Fig. 1.1a,b).



**Fig. 1.2a,b.** Rat embryo on day 18 of intrauterine life. **a** 1, Cortical plate; 2, intermediate zone; 3, subventricular zone. H&E,  $\times 200$ . **b** Mitoses in the cortical plate. H&E,  $\times 400$

The duration of the cycle is 7–10 h, while that of the S phase alone is 6 h. Later, these values increase to 20 and 10 h, respectively. The mitotic elements may begin to divide before reaching the luminal surface (subsuperficial prophase), where they complete the mitotic cycle, or they may complete division without reaching the luminal surface (nonsuperficial mitoses) [3228].

Still later, some cells no longer take up label. They enter a postmitotic phase and constitute young neurons which migrate to the marginal zone. This zone appears on the 13th day (in the rat) and progressively increases in thickness. On the 16th day, it divides into a superficial part, which will become the anlage of laminae I–VI (cortical plate), and a deep part, the subcortical zone, which will become the subventricular and intermediate zones (Fig. 1.2a). In these zones, the number of mitoses decreases from inside outwards (Fig. 1.2b). Between the 17th and 21st days of i.u. life, the neurons continue to migrate towards the cortical plate. In this plate there are initially no mitoses because neurons migrate after the cessation of mitotic activity. Later, mitoses appear in glial cells. The cells in contact with the pia in the marginal zone are glial in nature, a fact confirmed by their ability to express specific antigens such as glial fibrillary acidic protein (GFAP) and C1 [2787]. The subventricular and intermediate zones become the white matter. They contain astrocytic cells in mitosis. Glial cells are formed and they also migrate after neuronogenesis is completed.

There is a relationship between the time of migration of neurons and their subsequent localization in the cortex. Neurons which arrive first in the superficial part of

the marginal zone are displaced downwards by neurons arriving later, so that the pyramidal cells of the deep layers are those which matured earlier. However, this rule does not apply to the cells of Cajal–Retzius, the first cells to mature and place themselves in the marginal zone, where they subsequently form neurons with an as yet unknown function. In man, the Cajal–Retzius cells develop and mature before the neurons of the cortical plate arrive [502].

It is not known whether neurons and glial cells are produced by the same germinal cells, or whether they originate from different cells, even though they are histologically indistinguishable from one another [985, 3626, 3336]. The exact timing of divergence of the glial and neuronal cellular elements remains a matter of debate. According to His (1889) [1339], the germinal zone is composed of two cell lines: the *Keimzellen* or “germinal cells,” which will give rise to neurons, and the “spongioblasts,” which will give rise to the glia. Schaper (1897) [2972] was of the opinion that a single, mitotically active cell population produces “indifferent” cells. Upon migrating into the marginal zone, these give rise to neurons and glial cells. More recently, autoradiographic studies have demonstrated that in the germinal zone there is a homogeneous population of dividing cells, and that glial cells of a given structure are generated only after the production of neurons has ceased [986, 987]. The general concept is, therefore, that the matrix produces neurons first and later glia.

These concepts have been shaken by the observation that in rodents there are two cell populations with different generation times [3576]. Moreover, in monkeys the radial glia, or ependymoglia, and Bergmann’s glia already exist during the latest stages of neuronogenesis [2718, 2720, 3049]. The radial glia is situated in the ependymal layer and gives off long processes which reach the pia mater and the capillaries. This glia functions as a guide for the migration of neurons. The precursors of neurons and glial cells, therefore, coexist in the first stages of development. In *Macaca mulatta* it has been demonstrated that, by the 80th day of i.u. life, which corresponds to the peak of neuronogenesis, the germinal matrix contains a large number of proliferating GFAP-positive cells mixed with proliferating negative cells [1939]. Two mitotically active cell populations are, therefore, present at the same time. This has been confirmed by electron microscopy.

The localization of GFAP in cells that are actively dividing demonstrates that the acquisition of glial differentiation features by matrix elements is not incompatible with mitotic activity (Fig. 1.3). The coexistence of differently committed precursor cells in the fetal rat brain is supported by the observation that single embryonal cells, taken from the septal forebrain region of rat on the 14th day of gestation, give origin in microcultures to clones of neurons, glial cells, or both cytotypes. The heterogeneity of the clones probably depends on intrinsic properties of the precursor cells [3407].

Glial cells which have migrated into the intermediate zone, the commissures, and the fiber tracts continue to proliferate, whereas neurons do not. This finding is of great importance from the point of view of carcinogenesis.

Another still debated problem is the histogenetic relationship between astrocytes and oligodendrocytes, taking into account that, in broad terms, the latter do not appear in the neocortex before birth [666, 3332]. It has yet to be established whether the two glial types appear simultaneously or consecutively, and whether they derive from the same or from different precursors. In the corpus callosum of the mouse, oligodendrocytes have been observed to appear before astrocytes. They could have

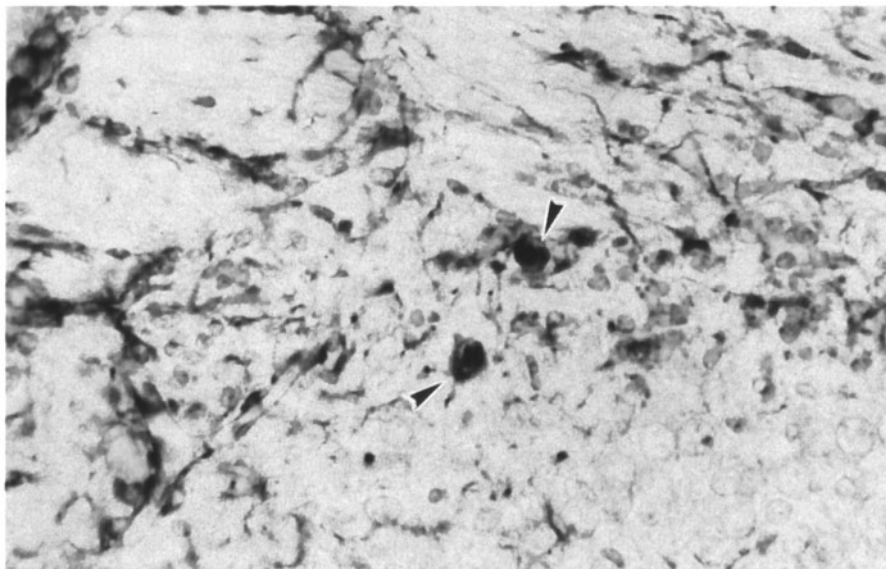


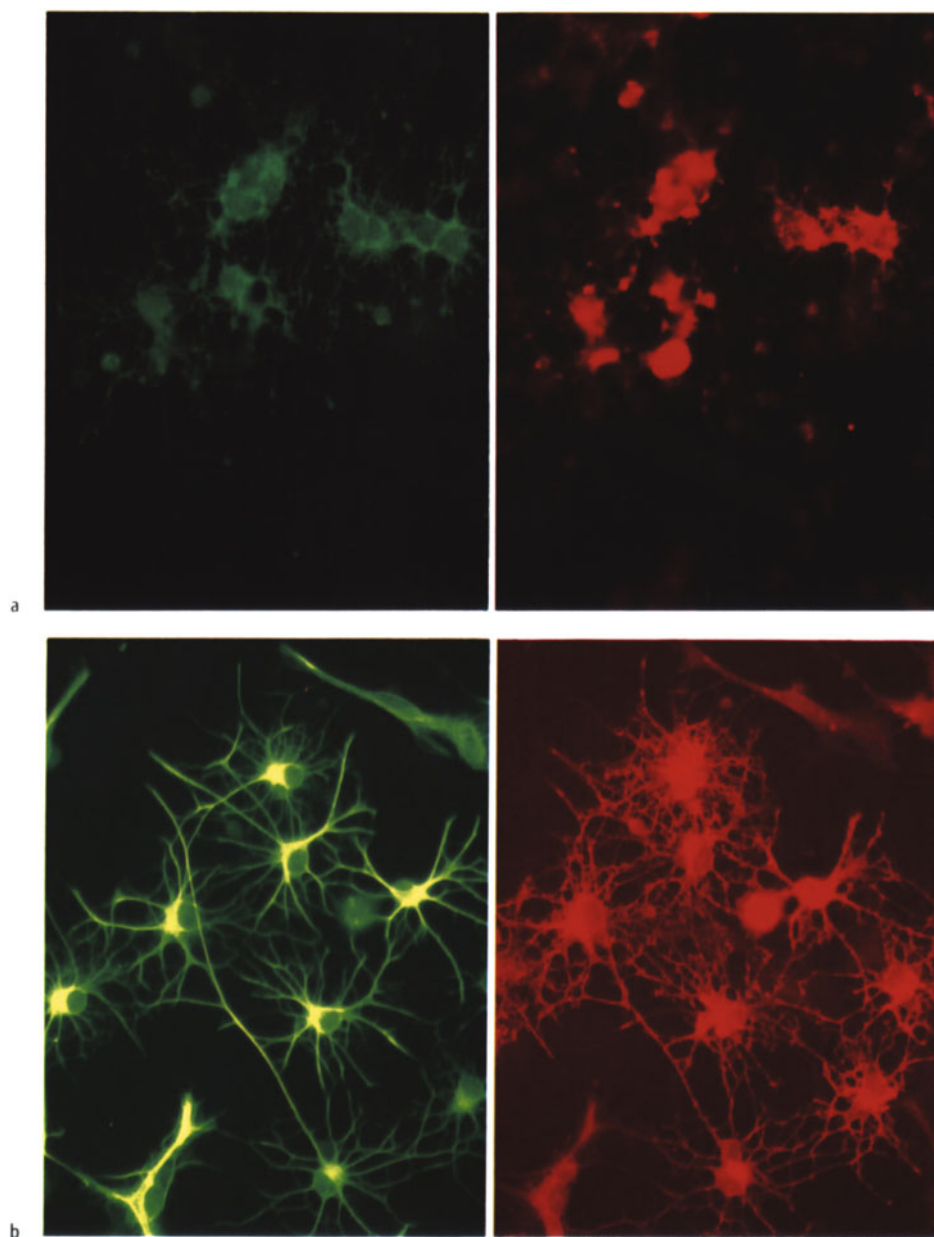
Fig. 1.3. Rat embryo on day 1 of extrauterine life. Glial fibrillary acidic protein (GFAP)-positive dividing cells. PAP-DAB,  $\times 1000$

either originated from different precursors or subsequently transformed into astrocytes [3229]. On the other hand, others have suggested that astrocytes arise before the oligodendrocytes [3528]. Less likely is the possibility that the two types of glia originate from different precursors [1491].

The differentiated oligodendrocytes are of three varieties: with a clear, an intermediate, or a dark nucleus [2319]. It is possible that these represent three stages of maturation, the first type deriving from oligodendroblasts which, in turn, arise from glioblasts. However, it is not known whether these glioblasts are identical to those which give rise to astrocytes [3332, 3213, 1458]. The differentiation of the oligodendrocytes is a postnatal process, but it has not been established whether it occurs in an identical fashion at all sites. Differentiation is connected with myelination, and, for example, it occurs earlier in the spinal cord than in the optic nerve. The period of rapid proliferation of the interfascicular oligodendrocytes in the first stages of development has been called myelination-gliosis [1491] and accompanies or precedes myelin formation. The optic nerve, which originates from the optic peduncle, an extension of the neural tube, represents an ideal site for the study of this problem. In fact, only astrocytes and oligodendrocytes (and no other type of glia or neurons) arise from the optic peduncle.

In short-term cultures, GFAP-positive astrocytes and galactocerebroside-positive oligodendrocytes are identifiable. In turn, the astrocytes are subdivided into two populations: types 1 and 2. These are different morphologically, antigenically, and in response to growth factors [165]. Astrocytes of type 2 are labeled by the monoclonal antibody A2B5. In the rat optic nerve, astrocytes of type 1 appear on the 16th day of gestation, oligodendrocytes on the first day after birth, and type 2 astrocytes between





**Fig. 1.4.** **a** Culture of neonatal rat cerebellum. The same cells are positive for A2B5 (*green fluorescence*) and chondroitin sulfate proteoglycan (*red fluorescence*).  $\times 1000$ . **b** Stellate astrocytes cultured from neonatal rat cerebellum are positive for chondroitin sulfate proteoglycan (*red fluorescence*) and for glial fibrillary acidic protein (GFAP).  $\times 1000$

the eighth and tenth day after birth [2706]. It has been observed *in vitro* [2706] that glial cells in the optic nerve develop along two distinct lines, one giving rise to type 1 and the other (O-2A) to type 2 astrocytes and to oligodendrocytes. The two lines diverge on the 17th day of gestation. The existence of two subpopulations of astrocytes, A2B5-positive and A2B5-negative, has been confirmed in optic nerve sections [2273]. Type 1 astrocytes give off processes towards blood vessels, and type 2 astrocytes to the nodes of Ranvier [165].

Oligodendrocytes originate from the A2B5-positive precursor called O-2A, as do type 2 astrocytes [165]. This precursor also expresses NG2 (the proteoglycan chondroitin sulfate) (Fig. 1.4a), but when reactivity for galactocerebroside appears, the former disappears [3280]. The same phenomenon has been observed in cultures of neonatal rat cerebellum; in the same model differentiated stellate astrocytes are positive simultaneously for GFAP and chondroitin sulfate proteoglycan (Fig. 1.4b) [1014]. NG2 has been shown to be a surface marker for a class of protoplasmic astrocytes in adults [1933].

Cultured precursor cells from the rat optic nerve differentiate into type 2 astrocytes only in the presence of fetal calf serum and, in contrast, precociously into oligodendrocytes in its absence [2706]. Platelet-derived growth factor (PDGF) regulates the proliferation of the precursor cell before differentiation takes place [2445, 2707] (see also Sect. 2.1). In fetal serum, factors are present which induce differentiation towards type 2 astrocytes. One of these is ciliary neurotrophic factor (CNTF) [165]. Type 1 astrocytes produce the A chain of PDGF [2784] and probably CNTF [165].

Under certain culture conditions, the cells may acquire intermediate phenotypes. This is a further demonstration that astrocytes and oligodendrocytes have a common progenitor and that environmental influences and developmental plasticity characterize their differentiation. Not only do astrocytes and oligodendrocytes have a common origin, but transitional forms may exist. In culture, if CNTF is lacking, precursors which had already acquired GFAP expression lose it and become oligodendrocytes [2703]. In the human fetus, at the 15th–16th week of gestation, cells with ultrastructural and immunocytochemical characteristics of oligodendrocytes have been described. These cells are, in fact, positive for myelin basic protein but also for GFAP [503]. This positivity is transient and disappears by the 17th–18th week of gestation.

The existence of “transitional” or “bipotential” forms of glial cells has been confirmed in cultures of human oligodendrocytes. After 2 weeks in culture, the cells express both GFAP and galactocerebroside. If, however, cyclic adenosine monophosphate (cAMP) and substances able to increase its level are added, the majority of cells become positive only for galactocerebroside [1675]. In the subpial astrocytes in the mouse spinal cord, an increased mitotic activity before myelination has, furthermore, been observed, and immediately thereafter oligodendrocytes appear. Finally, “transitional” cells with ultrastructural characteristics of oligodendrocytes may express GFAP [503].

The differentiation of precursor cells along the neuronal and glial lines is marked by the appearance of neurofilaments (NF) and GFAP. For the implication in neural carcinogenesis, it is important to emphasize that before NF and GFAP expression, precursor cells express Nestin, a new class of intermediate filaments. Nestin is expressed in 98% of the cells during development, but it is downregulated when NF

and GFAP are expressed [953]. It is reexpressed in primitive neuroectodermal tumors (PNET) and other tumors [3442].

## 1.2

### Gliogenesis in Adult Animals

Our knowledge regarding gliogenesis in the adult is incomplete. It is known that new glial cells may substitute those which degenerate; however, there is no evidence that death of glial cells occurs in the adult. On the other hand, in pathological conditions there may be hypertrophy and hyperplasia of astrocytes. It is not easy to understand how an increase in the number of astrocytes could take place in the adult. It was thought that this occurred by amitosis [2602], but this has not been confirmed. Glial cells are mainly diploid. However, polyploidy due to duplication of DNA without division of cytoplasm has been observed [1871]. It is not known whether the new glial cells originate from "stem cells" which remain quiescent under normal conditions, or if DNA synthesis may also occur in completely differentiated glial cells. In adults of different species, a glial turnover has been demonstrated.

In contrast to what occurs for neurons which rapidly become postmitotic, glial cells may continue to divide over time. A series of experiments has demonstrated that glial cells can proliferate postnatally [1427]. In the spinal cord of the rat, between 3 and 7 months there is an increase in the number of oligodendrocytes of about 15% per month, while the number of astrocytes remains at a constant level. The labeling index of glial cells in the white matter with [ $^3\text{H}$ ]thymidine is 12% after 4 weeks. After a month of continuous labeling starting from the age of 4 weeks, the oligodendrocytes in the spinal cord and in the cerebellum have an index of 20%, while in the same regions astrocytes have an index of only 10%.

In the final stages of embryonal development, a second layer of proliferating cells, localized between the ventricular germinal layer and the intermediate or mantle zone, is formed. This has been called the "subependymal zone" [1663], or "subependymal cell plate" [1101, 3227]. It progressively decreases with time and persists vestigially in the lateral ventricles of adult mammals (e.g., mouse, rat, dog, primates). It is, however, limited to those parts of the lateral ventricles underneath the neo- and paleocortex and not the archicortex. In the subependymal plate, mitoses are found (Fig. 1.5) but without movement of the nuclei in the interkinetic phase, and the generation time is 18 h [1943].

Very interesting studies have been carried out on the postnatal subependymal zone of the rat by stereotactic injection of replication-deficient murine retroviruses bearing reporter genes [1123]. The cells express Nestin, E-NCAM, A2B5, and CD3 ganglioside and migrate into the white matter, where they differentiate as oligodendrocytes, and into the gray matter, where they differentiate either as astrocytes or oligodendrocytes. The fate of the cells of the subependymal zone is restricted in vivo [1934]. At P14 they migrate into the white matter and become oligodendrocytes, but they do not migrate further into the cortex.

The cells migrate widely in a coronal plane and only for a limited extent antero-posteriorly. Migration probably takes place along radial glia.

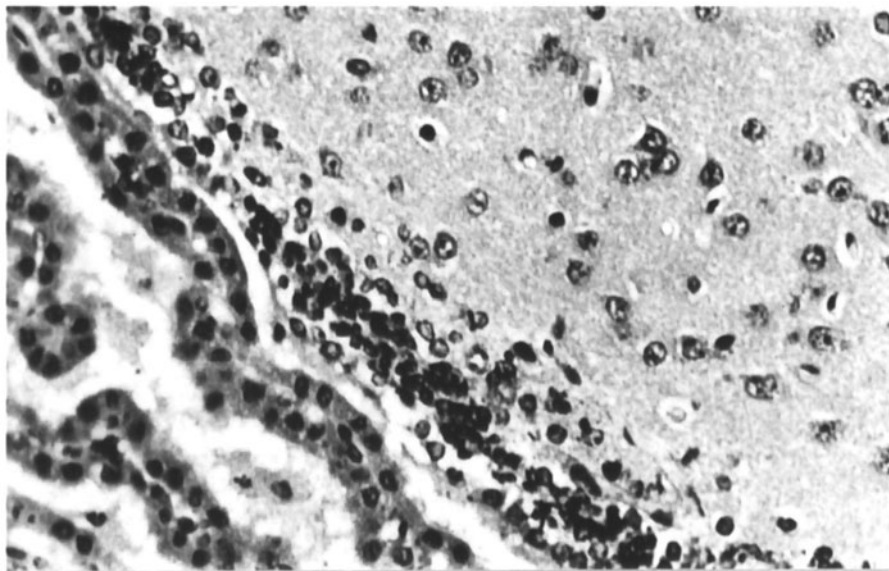


Fig. 1.5. Rat, subependymal plate. H&E,  $\times 400$

The subependymal plate in postnatal life may produce, for a short time, small neurons and glial cells in the adult. Its role may well be that of replacing glial cells in adult life.

Stem cells may be found in adult brains, apart from the subependymal plate, in the myelination glia, in the external granular layer of the cerebellum, in the fascia dentata, and in the subpial molecular layer of the cerebellum [1944]. The following scheme of differentiation of the subependymal layer has been proposed [1428]: The “stem cells” which migrate in the brain have a small, dark nucleus and give rise to glial precursors with small and clear nuclei. Twenty percent of these cells may transform into young astrocytes with a large and clear nucleus. The cells with a small and dark nucleus, however, may also be oligodendrocytes.

There is no general agreement that the subependymal layer is the continuous source of glial cells [2447, 1759, 1760]. In the mouse, labeled glial cells have been demonstrated within 1 h from the administration of  $[^3\text{H}]$ thymidine in all cerebral areas. Pairs of labeled cells have also been found. These findings demonstrate that, as stated above, proliferation may also occur in situ.

Though the glial turnover in the cerebral cortex, as compared to that of the white matter, is minimal [1759], the population is not static: 0.07% of glial cells are labeled 1 month after administration of  $[^3\text{H}]$ thymidine in the rat visual cortex. This implies that cell turnover is present, although slow and with a very long cycle [1588]. From double labeling experiments with  $[^3\text{H}]$ - and  $[^{14}\text{C}]$ thymidine, it has been found that the cycle time is 20 h. In the subependymal layer, around 30% of cells are in cycle, while in other parts of the brain no more than 1% of these cells are.

It would be of great importance to know not only if glial cells undergo mitosis, but also which type. Autoradiography cannot provide this answer, so great caution is ne-

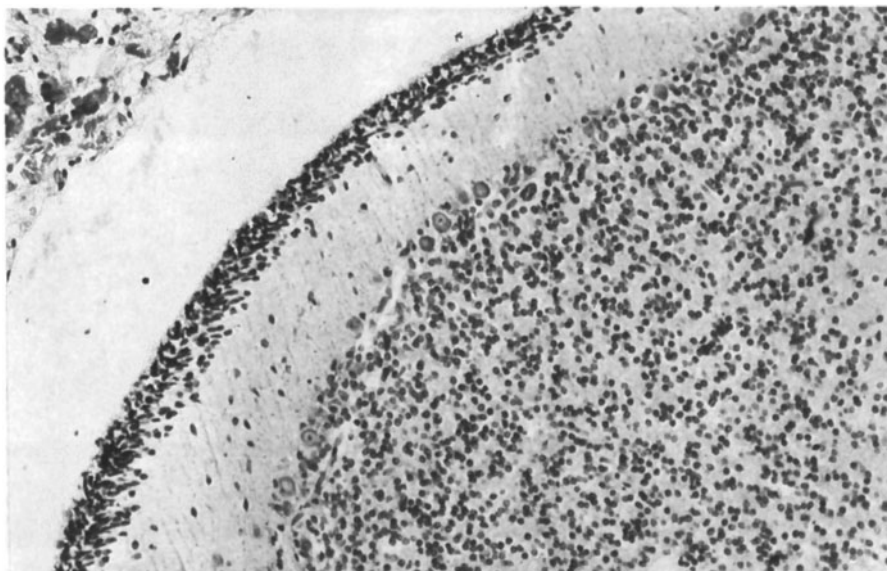


Fig. 1.6. Neonatal rat cerebellum, external granular layer. H&E,  $\times 200$

cessary in drawing conclusions [3335]. Furthermore, the difficulty in demonstrating mitoses, which are very sensitive to anoxia [457] and require particular fixation techniques for visualization, has to be taken into account. The fundamental fact remains that in the adult, outside the subependymal layer, mitoses are very rare [3333].

Evidence has been obtained by labeling cells using retroviral injection that immature, dividing cells remain in the adult white matter, do not express differentiation antigens, and do not migrate [1123].

### 1.3

#### Development of the Cerebellar Cortex

The development of the cerebellar cortex is a complex event because of the presence of two germinal zones. One is situated in the roof of the fourth ventricle and gives rise to Purkinje cells, to type II Golgi cells, and to a significant component of cerebellar glia. These migrate towards the pia mater to form the mantle layer. The other germinal layer, the external granular layer (EGL), is subsequently formed below the pia mater (Fig. 1.6). From it originate granule cells, stellate and basket cells, and glial cells of the molecular layer. This layer thickens in time, changing from one to six layers of cells because of cellular proliferation, and persists after birth, even if smaller, in many animals. In man, it only disappears 600 days after birth. At the beginning, 100% of cells of this layer become labeled with  $[^3\text{H}]$ thymidine, while subsequently an area devoid of mitoses is formed adjacent to the molecular layer. In the developing human cerebellar cortex, the neuronal types which are the progeny of the two different neuroepithelia, i.e., EGL and ventricular matrix (VM), are identified by

their immunoreactivity with class III  $\beta$ -tubulin isotype ( $\beta$ III) and calbindin-D28K.  $\beta$ III, which is one of the earliest-appearing markers of neuronal differentiation [799], is expressed early by EGL and stellate neurons, basket cells, and granules; while calbindin-D28K is expressed early by cells of the VM at the roof of the fourth ventricle and by Purkinje and Golgi II neurons [1607].

One of the unsolved problems is represented by the migration of the granule cells. Since it occurs late, it meets difficulties because other cellular elements are already fixed in place. The migration is guided by Bergmann's glia [2719]. It entails a complex adaptation of cellular shape. The more deeply situated cells in the layer are those which are generated first.

Glial cells seem to originate from the periventricular germinal matrix of the roof of the fourth ventricle. In the mouse, glioblasts from this matrix have already invaded the cerebellum when the migration from the external granular layer begins [988]. It is possible that glioblasts derive from the external granular layer, from which astrocytes and oligodendrocytes of the molecular layer originate, but that this occurs only after the production of neurons has ceased and, therefore, very late [704, 1017]. The same rule applies to the basket cells and to the small star-shaped cells.

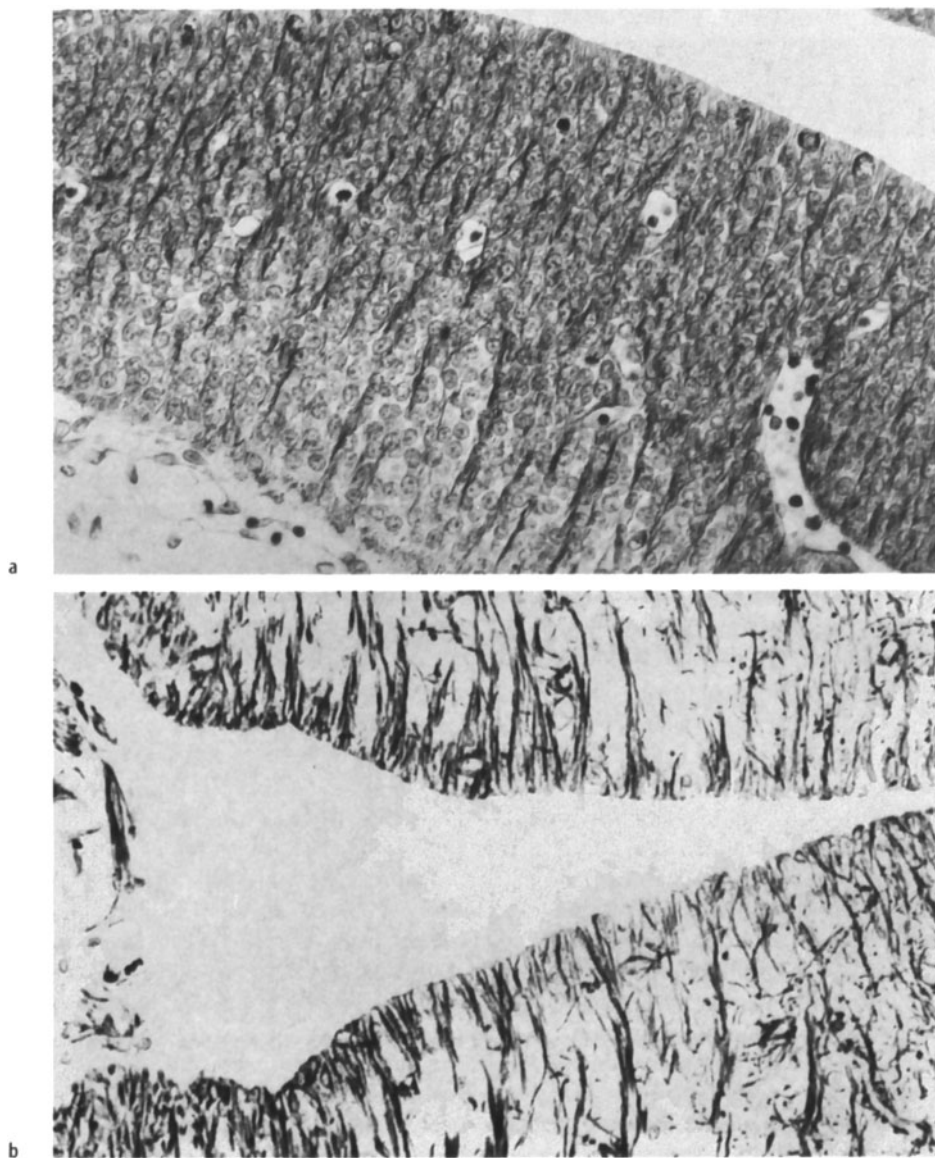
## 1.4 Radial Glia and Ependyma

Long, radially oriented fibers which span the whole thickness of the developing neural tube are present in the embryonal encephalon in very early stages of development. They have been demonstrated with the Golgi technique in many vertebrate species, including man, and have been variously called epithelial cells of Golgi [418], spongioblasts [3306, 2620, 3525], matrix cells [1261], ependymal cells [419, 2254, 3205], ependymoglia [966, 3334], ependymal spongioblasts [3413], and radial glia [2719, 2720, 3049, 3496, 793, 2066]. According to recent observations, the cells of the radial glia demonstrate mitotic activity at least at E13–E15 in the mouse [2286].

The presence of cells of the radial glia during the early phases of neurogenesis in man has been confirmed in studies combining silver and ultrastructural techniques with the demonstration of GFAP [73, 504]. In the human fetus, radial glia fibers have been identified from the 12th week of gestation by means of Golgi techniques, from the tenth week with the demonstration of GFAP, and from the seventh week with ultrastructural studies. The nuclei are initially situated in the ventricular zone, then in the subventricular zone, and less in the intermediate zone. The processes, sometimes with a subpial arborization, run from the ventricular zone to the pial surface, while some terminate on the blood vessel walls [504].

This and other observations [1762, 3331] seem to prove that in man the maturation of astrocytes with features of radial glia takes place in the first 3 months of fetal life. The production of glia, therefore, either precedes or occurs at the same time as that of neurons. It continues after the production of neurons has ceased [3049] and persists into late fetal development, by division both of cells of the subventricular layer and of cells which have already migrated to other regions.

A discrepancy exists between the positivity for GFAP of radial glia in primates and negativity in mice, rats and chickens [238, 3066, 3392]. When identifying GFAP in the



**Fig. 1.7. a** Rat embryo on day 14 of intrauterine life, vimentin-positive radial glia. PAP-DAB,  $\times 200$ . **b** Adult rat, glial fibrillary acidic protein (GFAP)-positive tanyocytes of the third ventricle. PAP-DAB,  $\times 200$

radial glia, the role played by species differences, mode of fixation, and procedures aiming at preserving the immunoreactivity of GFAP in the embryonal tissue has to be taken into account [501]. The radial glia in the rat is, instead, strongly positive for vimentin [241] (Fig. 1.7a). The positivity appears at the same time as that for neurofilaments in other structures and, therefore, may be indicative of differentiation. In

the rat, the precursors of glia and neurons may not express vimentin, as occurs in the chicken [3392]. A few short GFAP-positive fiber tracts with radial orientation have been observed in the rat embryonal brain at the 18th day of gestation [2651]. Cells and fibers marked by GFAP increase in number until the first postnatal week, in parallel with the disappearance of the radial glia.

Notwithstanding the fact that GFAP may be identified at an early stage, its appearance in great quantity occurs at the end of neuronal migration and the formation of long fiber tracts [3496]. At the same time that the GFAP increases in the fetal rat brain, a drastic reduction of vimentin and glial radial processes [2651] occurs. The time of maximum expression of GFAP and minimal expression of vimentin is at postnatal weeks 2–3, i.e., while the rapid myelination phase is in progress [635]. In adult rat glia, vimentin is very scanty unless the glia becomes reactive, hypertrophic, or hyperplastic [637, 3023]. The radial glia is GFAP-positive in the mouse spinal cord and is vimentin-positive in the whole brain [793]. The telencephalic radial glia of mice has been shown on cryostat sections to express GFAP by the 17th day of gestation [1218]. GFAP-positive radial fibers appear with a rostrocaudal and dorsoventral gradient during embryonal development, and disappear with the same gradient after birth, without correlations with the development of the cortex.

The role in guiding migrating neurons has been attributed to the radial glia both for the monkey [2718, 2720] and man [3188]. The rationale for this is its presence at the time of maximum neuronal migration and the close structural relationships between radial fibers and migrating neurons. The distribution of radial fibers is different in each area. Their orientation is modified during development according to morphogenesis in various areas and structures. A close correlation seems to exist between the position of a neuroblast in the ventricular zone and its final position. The concept of “proliferative unit,” meaning that all neurons are generated in the same position and guided by a single radial process, has been proposed [2721].

The radial glia seems, therefore, to have an important role in the embryonal development of mammals. It is also present in lower vertebrates, and while in these it persists after the end of development, it is found in adult life [1392, 3306]. In mammals, it transforms into other cellular types or degenerates [418, 2720, 504, 3049, 3128, 2651]. The transformation into protoplasmic and fibrous astrocytes has been observed in monkeys by means of silver impregnation techniques, showing intermediate forms between radial glia and astrocytes [3049]. The radial glia transforms first in the areas where cellular migration terminates first, i.e., at the same time its guiding role is completed [1938]. In the human fetal brain, between the 21st and the 30th weeks, the cytological basis of the transformation of the radial glia into astrocytes has been identified: increase in lysosomal activity and in the number of autophagic vesicles, which are necessary events for the reabsorption of the long processes [1565]. In the mouse, the predominant orientation of the mitotic spindle seems to indicate that the radial glia disappears through repeated divisions, with progressive detachment of the daughter cells from the cell attached to the pial surface [1218]. It has been hypothesized that oligodendroglia may also derive from radial glia, both directly and through intermediate astrocytic forms [505].

In the postnatal period of the mouse, the radially oriented fibers arising from the ventrolateral angle of the lateral ventricle persist [1218]. This is the zone in which cells retaining proliferative capacity in adult life are found [3229].



In the diencephalon, the radial glia undergoes minor modifications as compared with the other areas of the prosencephalon. In fact, the only zone of the mammalian adult encephalon in which radially oriented fibers may be observed is the hypothalamus, which belongs to the phylogenetically older part of the encephalon [3128, 1938]. This finding may be interpreted as representing a phylogenetic residuum of the diffuse system of radial glia which is present in lower vertebrates [1392].

The cells of the ependymal covering of the third ventricle, which are provided with a long process reaching the subpial layer, are called "tanycytes" (Fig. 1.7b). These cells also form the dorsoventrally oriented raphe fibers in the adult brain stem and spinal cord. The term "tanycyte" was initially used to indicate cells of the ependymal layer of the entire adult ventricular system of selachians, which is provided with a radially oriented process [1392]. Tanycytes are different from the cuboidal or columnar cells of the ependymal coverings in microscopic, ultrastructural, and histochemical properties [2275, 2276]. In the rat, they originate mostly in the postnatal period [51] or towards the end of fetal life [2912]. Their appearance is closely tied to the embryonal and fetal development of the ependymal covering.

The neuroepithelial cells which become ependymal cells begin to proliferate in the rat shortly after the formation of the neural plaque, i.e., before the tenth embryonal day [1758]. This begins on the 12th day in the mouse [2722]. In the rat, the production of ependyma proceeds with a caudorostral gradient, beginning on the 14th day in the fourth ventricle, on the 15th day in the third ventricle and on the 17th day in the lateral ventricles. It continues until the end of gestation, peaking at the 18th–19th day in the third ventricle and the 20th–21st day in the lateral ventricles [648]. The tanycytes, in contrast, are generated mostly in the postnatal period [51], even though they begin to appear during the last days of fetal life [2912]. In the rat, the tanycytes of the third ventricle do not mature completely until the third week after birth [2966, 2912, 361].

In human fetal brain, GFAP immunoreactivity of ependyma is detected as early as at week 8 of gestation; the entire ventricular ependyma is intensely stained by GFAP soon after differentiation from the primitive neuroepithelium [2953]. By term, scattered ependymal cells are still reactive [2953].

In the monkey, mouse, and rat the tanycytes of the third ventricle acquire GFAP in the embryonal period and keep it in adult life (Fig. 1.7b) [1938, 1218]. Human tanycytes, on the other hand, are only transiently positive for GFAP, between the 15th gestational week and birth [2814]. On the basis of these immunohistochemical data, tanycytes have been considered as a modified form of embryonal radial glia [1565], as a differentiated form of ependyma which develops in parallel with the normal ependyma [2814], or as astrocytic cells [684].

Most authors have not detected proliferative activity in the ependyma of the adult rat [364, 2722]. In the ependyma of the prosencephalon, there is a significant decline in proliferative activity in the first 2 postnatal weeks. The remaining cellular turnover is very low in adult life [484].

Even though tanycytes are considered to be specialized ependymal cells, their precise function is unknown. It has been proposed that they may form a connection between the cerebrospinal fluid (CSF) and the hypophyseal portal system [2003], transporting "hormones" secreted into the CSF to the anterior hypophysis [1720], in parallel with axonal transport, or conversely, to the CSF from the hypothalamic neurons

[3430]. Other functions have been attributed to tanycytes: regulation of ionic concentration in the extracellular periventricular spaces [1918], guides for migrating neuroblasts of the mediobasal hypothalamus as radial glia [3502], and a limiting barrier to the movement of neurohormones inside the compartments of the mediobasal hypothalamus [3502, 2768].

## 1.5

### Genes Controlling Nervous System Development

The development of the vertebrate nervous system is an exceptionally complex process, requiring the coordinated expression of a multitude of genes. The study of model systems such as the fruitfly *Drosophila* and the nematode *Caenorhabditis elegans* has provided invaluable information about the genetic mechanisms that control cell phenotype and segment identity during development. In fact, the genetic machinery controlling the invertebrate development is highly conserved in vertebrates and in humans, where it apparently plays a similar role. The first step in the development of the nervous system is the induction of the neural plate by uncommitted ectoderm in response to molecular signals from the adjacent mesoderm. The initially undifferentiated neuroepithelium then differentiates along the anterior-posterior, dorsal-ventral, and medial-lateral axes, giving rise to different neural structures composed of different classes of neurons and glia. The molecular control of these processes of morphogenesis and differentiation depends on a network of transcription factors that are expressed with high spatial and temporal selectivity for the control of cell lineage-specific genes.

Observations obtained in amphibians during gastrulation suggest that two proteins secreted by mesoderm, noggin and follistatin, act independently as inducers of neural differentiation in early ectodermal cells [1849, 1290]. Neural induction probably occurs in a subsequent step through a homeogenetic mechanism involving still unidentified molecules produced by neural plate cells (neural differentiation induced by neural cells) [2891].

In *Drosophila*, many of the genes that control the development contain the homeobox, a characteristic 180-bp sequence motif, and act as transcription factors. Several homologues of invertebrate homeobox genes have been identified in mammals, comprising mice and humans, and they are frequently involved in the development of nervous system [2210].

Mouse *Hox* genes, homologues of genes of the Antennapedia-Bithorax complex in *Drosophila*, play an important role in determining the regional identities of neural cells along the anterior-posterior axis within the hindbrain [1432, 2210]. Here the expression of specific *Hox* genes ends at the boundaries of transverse neuromeric domains called rhombomeres [2128, 2210]. Neuromeres are transverse segments of the neural tube with specific histogenetic and morphogenetic properties and a complete set of morphological longitudinal zones [2698].

Other homeobox genes have a role in controlling the development of most anterior regions of the nervous system. *En* genes, similar to the *Drosophila engrailed* homeobox gene, are normally expressed in the midbrain of mouse embryo, and *En-2* is necessary for the normal cerebellar development [1558]. Vertebrate homologues to

*wingless* gene of *Drosophila*, the *Wnt* gene family, encode putative secreted signal molecules and are expressed at several locations in embryonic mice and in the developing nervous system [2463]. Several observations suggest that *Wnt* genes are involved in inducing specific cell fates in a regional manner and at different time points in embryogenesis. In particular, inactivation of mouse *Wnt-1* gene, the prototype member of this family, produces defects in development of the midbrain and the cerebellum; in extreme cases, animals lack the entire cerebellum and a significant portion of the midbrain [2218]. The *Wnt* family is particularly interesting because two members, *Wnt-1* and *Wnt-3* genes, were first recognized as proto-oncogenes activated in mouse mammary tumors; the homology with *Drosophila wingless* was not shown until later [2813]. Members of the *PAX* domain gene family are expressed in different regions of the nervous system during development, including forebrain structures. *Pax-5* is involved in midbrain development, as its inactivation leads to hypoplasia of the inferior culliculum [3489]; inactivating mutation in the *Pax-6* gene of mouse determines defects of neuronal migration with increased volume of forebrain germinal zone, heterotopias, and cortical malformations [3047].

Different families of homeobox genes, as well as other regulatory genes, display restricted temporal and spatial patterns of expression in the embryonic forebrain, suggesting a central role in specifying identity of diencephalic and telencephalic structures. These include homologues of the *Drosophila* genes, *distal-less* (*Dlx-1* and *Dlx-2*) [380], *empty spiracle* (*Emx-1* and *Emx-2*) [3196], *NK-2* (*Nkx-2.1*, *Nkx-2.2*, *Nkx-2.3*, and *Nkx-2.4*) [2688], *orthodenticle* (*Otx-1* and *Otx-2*) [3196], four members of the *Wnt* family (*Wnt-3*, *Wnt-3a*, *Wnt-5a*, and *Wnt-7b*) [2218], *POU* domain genes [2843], *Gbx* [380], *Dbx* [2032], and some helix-loop-helix genes, such as *N-myc* [821]. All these genes are expressed in spatially restricted patterns with regard to longitudinal and transverse domains in the neural tube. However, they are also differentially expressed in the wall strata of the embryonic neural tube. For example, *Gbx-2* is expressed primarily in the mantle zone (i.e., in differentiating cells), while *Wnt-3* is expressed in both the mantle and the ventricular zone (i.e., in undifferentiated, mitotically active neuroepithelial cells) of the mouse dorsal thalamus [380]. The expression patterns of all these regulatory genes suggest a neuromeric organization of the embryonic forebrain, similar to that described for rhombencephalon [2698].

*Gtx*, a homeobox gene with a sequence divergent from the *Hox* class genes, shows a different expression pattern. It is expressed more abundantly in the mouse adult brain than in fetal or neonatal brain, and its expression in adult CNS seems specifically restricted to glial cells [1742]. These data suggest that *Gtx* is involved in the control of differentiation of glial cell lineages acting as a "cell-type specification" gene.

Several polypeptide growth factors are involved in the control of growth and differentiation of glial cells, including CNTF, glial maturation factor (GMF), insulin-like growth factor (IGF), interleukin 1 (IL-1), PDGF, and tumor necrosis factor (TNF) [1492].

The multifunctional cytokines of the family of insulin and IGF, as well as their receptors, are diffusely expressed in the developing CNS [679]. The expression of IGF-I, IGF-II, and of IGF-binding proteins (IGFBP) is temporarily and spatially restricted, with an association of IGF-I with neuronal cells, of IGF-II with non-neural elements, and of IGFBP with neurons and glial and mesenchymal cells. In contrast, receptors for insulin and for IGF show widespread and overlapping expression in the

developing and adult CNS. Moreover, there is evidence for the presence of preproinsulin gene transcripts in CNS early on in development [679]. Even though their role is not yet fully clear, IGFs might represent important autocrine and paracrine signals in CNS development. Interesting information comes from observations made in knockout mice for IGF-I, IGF-II, and IGF receptor [1988]; these are dwarf mice which show a generalized delay in development, demonstrating that this growth factor loop is required to obtain normal size and cytoarchitecture of the CNS [679].

PDGF is implicated in mechanisms of glial differentiation, and it has been shown to play a key role in the proliferation and differentiation of glial cell lines of the optic nerve [2784, 2445, 2707, 2693]. The proliferation of the bipotent O-2A progenitor, which gives rise to oligodendrocytes and to type 2 astrocytes of the optic nerve, is induced by PDGF, which is produced by type 1 astrocytes. In the absence of PDGF, the O-2A progenitors differentiate precociously, and PDGF is thus crucial for the control of myelination in the CNS [2703]. A similar process may also occur in cerebellum [45]. In fact, PDGF  $\alpha$ -receptor is expressed in developing rodent nervous system only by glial cells [3751] of the oligodendrocyte lineage [2694] and PDGF A chain gene is highly expressed in neurons of developing and mature mice [3750]. The temporal coordinate expression of these two genes during late embryogenesis and in early post-natal life indicates that neurons may direct glial cell development by a paracrine mechanism.

## Factors of the Transformation Process

### 2.1

#### Genetics and Molecular Biology

The technological advances in molecular genetics which have been made from the middle of the 1980s onwards have permitted a new approach to the study of carcinogenesis and are also providing a remarkable and promising volume of data on CNS tumors. The reader is referred to specialized publications on the theoretical basis of biology and molecular genetics. In this chapter, an overview of the most recent discoveries in this field relating to CNS tumors is presented.

Increasing evidence suggests that tumorigenesis is a multistep process requiring the accumulation of distinct mutational events in target genes. In some instances these genetic changes are inherited, while in others they occur randomly or are induced by different agents. At least two types of genetic alterations and of target genes can be involved in cancer initiation and progression, i.e., recessive mutations inactivating tumor suppressor genes and dominant mutations activating proto-oncogenes. The retinoblastoma susceptibility gene (RB1), the first tumor suppressor gene to be discovered, can be considered paradigmatic. Retinoblastoma may be sporadic, but in 40% of cases is familial and transmitted as an autosomal dominant trait. Epidemiological considerations have suggested that retinoblastoma may represent the result of two separate mutations [1724]. The first, i.e., the “predisposing” mutation, may be inherited with germ cells (heritable cases) or acquired somatically in single cells of the retina (in sporadic cases). In either case, this first mutation is insufficient to cause the tumor, which is produced only after a second genetic alteration affecting the remaining normal allele in the same retinoblastoma locus. The probability of occurrence of the second mutation is very high. In fact, in 90% of those individuals who have inherited a defective gene, retinoblastoma will develop, frequently as bilateral or multicentric tumors [971]. It is, therefore, understandable that the “predisposing” mutation, even if transmitted as a dominant trait, is in reality recessive at the cellular level. Cytogenetic investigations and studies carried out with restriction fragment-length polymorphism (RFLP) analysis have led to the localization of the retinoblastoma locus (RB1) on the q14 band of chromosome 13 [458, 459, 768]. Thus the RB gene behaves as a suppressor or repressor of tumor development, or as an “antioncogene” [1725], and its loss or inactivation leads to the development of the tumor. Different chromosomal mechanisms may be responsible for homozygosity of the mutant RB1 gene in tumors, such as nondisjunction, nondisjunction with duplication, mitotic recombination, small deletions, and point mutations [459]. When analyzed with molecular genetic techniques, the great majority of hereditary retinoblastomas have

shown chromosomal aberrations affecting the wild-type RB allele on chromosome 13 and consisting in loss of the chromosome, without or with reduplication of its homologue, or mitotic recombination involving its long arm [458, 459].

RB1 was isolated in 1986 [971, 1896, 1000]. The gene, composed of 27 exons, extends for more than 200 kilobases (kb) and produces a transcript of 4.7 kb, coding a 105- to 107-kDa nuclear phosphoprotein with DNA-binding capability [972]. The availability of the gene has led to a more precise description of the mutational events affecting retinoblastoma genes. In both forms of the disease (hereditary and sporadic), a variety of different mutations have been described, ranging from subtle base changes to large deletions and mimicking of spontaneous mutagenesis mechanisms [1042]. The biochemical mechanism by which the product of the RB gene exerts its antioncogenic effect is unknown, but its ability to bind DNA suggests that it participates in the control of the transcription or replication of DNA. In fact, the levels of phosphorylation of the RB1 gene product are variable during the cell cycle, increasing in the S and G<sub>2</sub> phases [566, 488]. Moreover, it has been shown that some viral transforming oncoproteins, such as the large-T antigen of SV40, the E1A of adenovirus, and the E7 protein of human papillomavirus, form stable complexes with the RB1 protein [3668, 2035, 797]. This finding suggests that the tumor suppressor activity of the RB1 gene product may be abolished by different mechanisms comprising the binding with retroviral oncoproteins. The primary role in retinoblastoma tumorigenesis of inactivation of the RB1 tumor suppressor activity is also demonstrated by the observation that reintroduction of the missing RB1 gene into various RB1-deficient tumoral cell lines changes neoplastic morphology and reduces growth rate and tumorigenicity both *in vivo* and *in vitro* [1425].

Inactivating mutations of the RB1 gene have been observed in various tumor types [195, 3100], in agreement with the observation that children surviving hereditary retinoblastomas have a very high likelihood of developing a second, different tumor, particularly osteosarcomas, but also brain tumors [824]. In fact, cytogenetic and molecular studies have shown that deletions of 13q frequently occur in high-grade astrocytomas [1497, 997, 2729]. Two studies have demonstrated loss of heterozygosity (LOH) at the RB1 locus in approximately one third of high-grade astrocytomas, and in some of the tumors showing LOH, mutations inactivating the remaining allele were detected [3538, 1298]. Since deletions and mutations at the RB1 locus have been found only in anaplastic astrocytomas and glioblastomas, it is probable that RB1 inactivation is one of the pathogenetic mechanisms involved in astrocytoma progression. Pinealoblastoma is the second brain tumor that may be associated with inherited retinoblastoma in so-called trilateral retinoblastoma [121], suggesting a possible common origin from RB1 gene inactivation. In agreement with this hypothesis, experimental data have shown that mice harboring inactivation of RB1 and p53 genes develop pinealoblastomas in 40% of cases [3682].

Following the isolation of the Rb1 gene, at least 11 other tumor suppressor genes were identified, and some general observations can now be made about this group of genes [1782, 1931, 3217]. Tumor suppressor genes are normally involved in control of cell proliferation (inhibition of growth) and differentiation in different tissues, so that the mutation of a single tumor suppressor gene can predispose to various tumor types. Moreover, tumor suppressor proteins may have different functional properties; the product of RB1 gene is a nuclear transcription factor; neurofibromin (the product

of neurofibromatosis-1 gene, NF1) is a cytoplasmic GTPase-activating protein (GAP) involved in signal transduction, while the product of von Hippel-Lindau (VHL) gene may act regulating transcription elongation [1790].

At least four other known tumor suppressor genes are involved in brain tumor initiation and progression: NF1, NF2, VHL, and p53 genes.

Linkage studies in pedigrees affected by the peripheral form of neurofibromatosis (NF1) have led to the localization of the genetic defect in this disease to band 17q11.2 [150, 1120]. The gene responsible for NF1 has been isolated subsequently by means of positional cloning techniques [462, 3557, 3596, 1206].

This gene, composed of at least 59 exons, extends for more than 350 kb on the long arm of chromosome 17 [1950]. It encodes a large transcript of approximately 13 kb and a protein, termed neurofibromin, that contains 2818 amino acids and is ubiquitously expressed [209, 210, 1950, 2106]. A small portion of neurofibromin shows significant homology with the catalytic domain of a family of GAP proteins [365, 3734]. GAP proteins inactivate the product of the *ras* proto-oncogene, promoting the conversion from the active dimer *ras*-GTP to the inactive form *ras*-GDP. The interaction of the NF1 gene product with *ras* suggests a role in controlling signal transduction related to proliferation and differentiation and is consistent with a tumor suppressor activity [2250]. However, recent experimental observations [1548, 1549] indicate that, in some cell types, the tumor suppressor function of NF1 may be independent of its GTPase-accelerating activity.

Detection and characterization of germline mutations in NF1 patients is difficult owing to the large size and complex organization of the gene [3488]; thus the correlation between gene mutations and diverse phenotypes of neurofibromatosis has still to be elucidated [2250]. In contrast, the role of this gene as a tumor suppressor in the development of tumors associated with NF1 has been indicated by the demonstration of somatic mutations in many tumors [1904, 1949, 3135, 3735]. Until now, only very rarely have mutations of NF1 gene been detected in sporadic glial tumors [1949, 3408], despite the predisposition of NF1 patients to develop gliomas. Interestingly, in tumors associated with NF1, constitutional LOH for NF1 locus was found only in malignant lesions and has not been demonstrated in benign neurofibromas [3216, 1370], suggesting that the wild-type copy of NF1 is retained in these tumors. It appears that all the features of von Recklinghausen disease cannot be attributed solely to mutations in the NF1 gene, and epigenetic mechanisms affecting gene transcripts may also be involved [2250].

One of these epigenetic mechanisms may be devoted to the regulation of neurofibromin expression by alternative splicing of NF1 transcripts. In fact, four transcripts have been identified which differ by alternate splicing of exon 23a (type I and II mRNA) or exon 48a (type III and IV mRNA). The different NF1 mRNA isoforms are differentially expressed: type I transcript is predominantly expressed in fetal brain and in undifferentiated cells, while type II mRNA is expressed preferentially in differentiated cells [2434]. Moreover, brain tumors preferentially express type II isoform, whereas type I is the predominant isoform in normal adult brain [3347]. A second epigenetic mechanism potentially involved in regulation of NF1 expression is RNA editing, a post-transcriptional site-specific modification of mRNA. Edited NF1 mRNA, harboring a C-to-U transition at position 2914, has been detected in all normal human tissues tested, but levels of editing were significantly higher in NF1 tu-

moral tissues than in cells from normal individuals [2250]. The modification induced by mRNA editing at position 2914 may be functionally important involving the protein domain essential for interaction with *ras* [2250].

A common tumor suppressor gene is involved in at least a part of the different tumors of the nervous tissue which appear in NF2 [3177, 2022]. In this hereditary autosomic dominant condition, multiple tumors originating from different types of cells may arise, such as bilateral acoustic neurinomas, multiple spinal, peripheral, or cranial nerve neurinomas, meningiomas, and gliomas. Monosomy, deletions, or LOH for the long arm of chromosome 22 are also common findings in sporadic neurinomas [3118, 583, 925] and meningiomas [3773, 387, 3119, 790] as well as in ependymomas [2729, 1499] and in astrocytomas [1278, 3420, 1353]. From the mid-1980s, molecular genetic studies suggested that NF2 is located on the long arm of chromosome 22 [3119]. Linkage analysis of a large family has subsequently localized the NF2 locus to the region 22q11.2 [2857, 3649], and in 1993 further investigations led to the cloning and sequencing of the gene responsible for the disease [2858, 3459].

The NF2 gene encompasses 110 kb and is composed of 17 exons, one of which is alternatively spliced [2022]. Transcripts of three different sizes are widely expressed in normal human tissues, including brain, as well as in fetal mouse nervous tissue [2858, 3459]. The protein encoded by NF2 gene, merlin, shares homology with a highly conserved family of proteins which are thought to create a link between integral proteins of the cell membrane and intracellular cytoskeletal components [3459]. It has been postulated that merlin is involved in pathways addressing growth inhibitory signals from the cell surface to intracellular structures [2022].

Several germline and somatic mutations have been detected in NF2 gene, mostly leading to a truncated inactive merlin [2022]. Recent data suggest that, in NF2 patients, a more severe phenotype is associated with grossly truncating mutations [2246]. Mutations of the NF2 gene are present in over 50% of schwannomas comprising sporadic cases [254, 1471, 1913, 2918, 3475], often associated with demonstrated allelic loss in the other chromosome 22. Immunohistochemical analysis using antibodies against merlin has demonstrated inactivation of NF2 protein in these tumors, showing complete absence of staining in tumor Schwann cells in contrast to staining in normal vestibular nerve [2918]. Similar results have been obtained studying sporadic meningiomas; NF2 tumor suppressor gene is probably involved in approximately 60% of all meningiomas, with a preference for fibroblastic tumors compared with meningothelial ones [1913, 2911, 3642]. In the remaining 40% of meningiomas, other non-NF2 genes are probably involved, with the possibility of a second meningioma locus on chromosome 22q [2911, 2629]. Starting from the observation that sporadic ependymomas and astrocytomas show frequent allelic losses of chromosome 22q, commonly encompassing the NF2 gene, studies have been carried out to investigate the possible involvement of NF2 gene in these tumors. However, only a single mutation was detected in one out of seven ependymomas [2888], whereas none of 30 fibrillary astrocytomas [2888] and 70 gliomas, including astrocytomas, anaplastic astrocytomas, glioblastomas, oligodendrogliomas, and oligoastrocytomas [1353], had a detectable somatic mutation in NF2 tumor suppressor gene. These results suggest that NF2 gene may be involved in tumorigenesis of some ependymomas, while a different tumor suppressor gene located on 22q is probably inactivated in astrocytomas.



The VHL susceptibility gene was identified in 1993 [1879], following its localization on the short arm of chromosome 3 (3p26) [3121, 3774] by linkage analysis. Human VHL gene contains three exons and a long 3' untranslated region. It encodes a protein of 213 amino acids with no significant homology to any known proteins [1879]. Even though transcripts of VHL gene can be detected in a variety of tissues, the protein has not been identified in human tissues [2408]. Germline mutations in VHL gene have been demonstrated in the majority of VHL kindreds [487, 606]; they are scattered throughout the gene and are frequently predicted to produce a truncated protein. There is a correlation between phenotype and the type of mutations detected; 96% of VHL families with pheochromocytoma have missense mutations, whereas in families without pheochromocytoma, large deletions, microdeletions/insertions, and missense and nonsense mutations are detectable [2408]. As expected in the case of inactivation of a tumor suppressor gene, tumors associated with VHL, including cerebellar hemangioblastomas, show LOH at the VHL locus with retention of the mutant allele. Moreover, somatic mutations of this gene have been described in sporadic cerebellar hemangioblastomas [1586], similar to clear cell renal carcinomas [1104, 3186]. Interestingly, a second mechanism of VHL gene inactivation has been described in sporadic clear cell renal carcinomas, consisting in hypermethylation of exon 1 [1302].

Recent studies [770, 1668] have suggested a possible mechanism of action of the VHL tumor suppressor gene. The normal product of VHL gene was shown to inhibit the activity of the transcriptional elongation factor named elongin, binding to its subunits B and C. In patients harboring defective VHL genes, elongin is not negatively regulated by the VHL gene product, resulting in excessive elongation of transcription and a high transcript level of as yet unidentified target genes [1790]. This mechanism may be extremely important, as the regulation of several oncogenes, including *c-myc*, is exerted at the level of transcript elongation [1790].

Mutations of the p53 tumor suppressor gene are the most frequent genetic abnormalities in human cancer; in about half of all cancer cases, the two p53 alleles are mutated or deleted [1376, 1932]. The p53 gene, composed of 11 exons, is located on the short arm of chromosome 17. It encodes a tetrameric phosphoprotein that binds to specific DNA sequences and activates the transcription of genes containing p53-binding sites [3560]. Most p53 mutations detected in human tumors occur in exons 5–8, within the most conserved domains of the gene [1376], affecting the DNA-binding capacity of the protein and probably leading to the loss of its transcriptional activity [500]. Wild-type p53 plays a central role in a number of cellular processes related to cell growth control. In several systems, p53 suppresses transition from G<sub>1</sub> to S phase of the cell cycle [734, 1802, 2133], and a considerable amount of evidence indicates that the arrest of cell cycle progression is obtained by inducing the expression of a cell cycle inhibitor named Cip1 [811, 789]. p53 induces cell cycle arrest in response to DNA damage [1603], while in absence of p53 action the frequency of DNA rearrangements is enhanced and the genome becomes unstable [1989, 3752]. Following these observations, p53 has been described as a “guardian of the genome” [1859]. One possible outcome of the arrest of cell cycle induced by p53 is apoptosis [1859]; this is dependent on p53 in the case of DNA strand breakage caused either by ionizing radiation or chemical agents, but not in other cases [2027, 529].

The role of p53 as a tumor suppressor gene has been widely confirmed; wild-type p53 has been shown to inhibit neoplastic transformation and growth in vitro and in

vivo, while this antitumor response is not produced by p53 mutants [1932]. Moreover, transgenic mice lacking p53 are significantly predisposed to spontaneous development of tumors at early age [750]. Germline mutations of the p53 gene have been detected in members of families with Li-Fraumeni syndrome, a familial cancer syndrome predisposing to soft tissue sarcoma, breast carcinoma, glioma, osteosarcoma, leukemia, lymphoma, and adrenocortical carcinoma [2081]. In contrast to other tumor suppressor genes, the mutation of a single allele of p53 may have a negative dominant effect, complexing to the normal p53 and inhibiting its function. This dominant negative effect is exhibited variably by the different p53 mutations and is not produced by mutations resulting in protein truncation [3560]. Further mechanism of inactivation and accumulation of p53 consists in overexpression of the MDM2 oncogene, an upstream negative regulator of p53 [2492].

Several studies indicate that mutations in p53 gene frequently occur in human astrocytic gliomas [2428, 521, 1269, 998, 2140, 947, 3565, 2962, 703, 3409, 3513, 3514], while they are uncommon in other nonastrocytic brain tumors, such as oligodendrogliomas, ependymomas, medulloblastomas, and primitive neuroectodermal tumors (PNET) [2479, 2963, 2710, 3724, 170]. Mutations have been found in approximately one third of fibrillary astrocytomas, anaplastic astrocytomas, and glioblastomas [2012], mainly consisting in missense mutations in the conserved domains of the gene, with “hot spots” including codons 175, 248, and 273. Pilocytic astrocytomas do not generally show p53 mutations [516, 1434, 2480, 3724, 1862, 1983, 2736, 3038]. The frequency of p53 mutations seems to correlate with patient age, in that they are less frequent in patients older than 40 years [516, 2020, 2736]. In malignant astrocytomas of childhood, mutations have been found infrequently [2021, 3782, 2736, 3038].

Thus p53 mutations occur early in the tumorigenesis of astrocytic tumors, i.e., they are associated with neoplastic transformation of astrocytes. In recurrences of low-grade astrocytomas that originally did not carry p53 mutations, no new mutations have been detected, even in the presence of a malignant phenotype in the recurrent tumor [3513]. Apparently in contrast with these data is the observation of clonal expansion of subpopulations of mutant p53 during malignant progression of astrocytomas [3189].

There are conflicting results about the occurrence of germline p53 gene mutations in families predisposed to develop gliomas, in the absence of the complete Li-Fraumeni phenotype. While some authors have not found p53 germline mutations in glioma families [3514, 2014], others have detected such mutations in a family with a predisposition for astrocytomas [2033] and in particular subsets of glioma patients [1832]. In the latter study, the group of patients showing germline p53 mutations included subjects with multifocal glioma, glioma with another primary malignancy, and glioma associated with a family history of cancer. Mutations were particularly frequent if these three factors were combined; however, the distinction from Li-Fraumeni syndrome of at least some of the families described in the study is not sharp enough for conclusions to be drawn about the frequency of germline p53 mutations in glioma families.

Immunohistochemically detectable nuclear accumulation of p53 occurs in about two thirds of anaplastic astrocytomas and glioblastomas, while in one third of fibrillary astrocytomas there are scattered p53-positive cells [148, 1512, 1207, 1591, 2020,

2420, 516, 1775, 3254, 819]. The accumulation of p53 frequently occurs without p53 gene mutation and is not correlated with survival [516, 1775, 3514, 2736, 819], even though a slight positive correlation with proliferation indices has been observed [148, 1207, 819]. Taking into account the fact that overexpression of MDM2 gene in astrocytomas is rare [2962, 2420, 2755, 2887, 2736], nuclear accumulation of wild-type p53 is probably a physiological response to DNA damage that accumulates in higher-grade tumors. In association with overexpression of wild-type p53, astrocytic gliomas express *bcl-2*, which is known to inhibit apoptosis mediated by p53 [32]. Overexpression of p53, revealed by immunohistochemistry, has been proposed as an indicator of poor prognosis in PNET patients [1513]. In this study, intense immunoreactivity to p53 led to identification of a group of PNET patients with a relative risk of death sevenfold higher than in other patients.

The possible involvement in brain tumors of another tumor suppressor gene, adenomatous polyposis coli (APC), has recently been investigated. APC gene mutations were identified in patients with familial adenomatous polyposis as germline mutations and also in sporadic colorectal adenomas and carcinomas. The same germline mutation has subsequently been identified in patients with Turcot syndrome (polyposis coli together with malignant gliomas or medulloblastomas) but, surprisingly, APC mutation was not found in 91 patients with sporadic neuroepithelial tumors [2320]. However, in a recent study [1231], germline mutation of APC gene and loss of the remaining normal allele on the homologue 5q chromosome have been demonstrated in a medulloblastoma in a Turcot patient. Moreover, in other Turcot families the germline mutation was identified in the genes *hMLH1* or *hPMS2*, which are normally involved in the repair of DNA mismatches [1231].

The possible presence of a tumor suppressor gene on a particular chromosome is suggested first at all by the identification of specific nonrandom rearrangements or deletions. In fact, karyotypic analyses and molecular studies of allelic loss have provided useful tools for localizing such genes. Several cytogenetic analyses have demonstrated frequent nonrandom numerical and structural chromosomal abnormalities in human gliomas [249, 1536, 252, 2941, 2734, 2771]. Numerical changes consist preferentially in gain of chromosome 7 and in losses of chromosomes 10, 22, and sex chromosomes. Structural rearrangements are common in chromosomes 1p, 9p, 7q, 19q, 17p, 3, 6, 8, and 11 both in low- and high-grade astrocytic tumors. With increases in the degree of malignancy, chromosomal anomalies generally become more marked and involve greater numbers of different chromosomes [3137, 246]. In the more malignant gliomas, therefore, it is difficult to evaluate which chromosomal anomalies are specific and significant in the genesis of the neoplasia and which are nonspecific epiphenomena which accompany the process of anaplasia.

Rearrangements involving the short arm of chromosome 9 are very common in anaplastic astrocytomas, and allelic losses of 9p regions have been detected in at least one third of anaplastic astrocytomas; these are rare in low-grade tumors [1500, 2495]. In the short arm of chromosome 9, a tumor suppressor gene, *CDKN2* (or *MTS1*), is located that is deleted in a great number of tumor cell lines, including 80% of astrocytoma lines [1577, 2446]. *CDKN2* encodes p16, a cell cycle-regulating protein that inhibits CDK4/cyclin D phosphorylation of RB protein. Mutations of this gene are rare in primary astrocytomas with allelic 9p loss [3484, 1071]. However, homozygous deletions seem to be frequent in anaplastic astrocytomas and in glioblastomas.

blastomas [1071, 1533, 3055, 3594], suggesting that mutation of another tumor suppressor gene on 9p is associated with astrocytic tumors, even though CDKN2 inactivation may contribute to the acquisition of malignant phenotype in these tumors. Moreover, amplification of the CDK4 gene has been detected in approximately in 15% of glioblastomas [3055].

Partial or complete allelic loss for sequences on chromosome 10 has been demonstrated in 60%–85% of glioblastomas and only rarely in anaplastic astrocytomas [997, 1497, 983, 3616, 2735, 1598], suggesting a critical role in late stages of malignant progression of astrocytomas. Shorter survival and older age at diagnosis have been observed in patients with malignant gliomas showing LOH on chromosome 10 [1900]. Deletion mapping analyses [2735, 1598, 3287] have suggested the existence of at least two different tumor suppressor genes on chromosome 10, the first is localized in the 10q24 to 10q26 region, and the second on the short arm or centromeric region of chromosome 10 (10pter–10q11). In agreement with the existence of one or more tumor suppressor genes on chromosome 10 is the demonstration that the introduction of a copy of this chromosome into the U-251 glioma cell line abolished their tumorigenicity in nude mice [2619].

Deletions of chromosomes 22q and 13q referring to NF2 gene mutations and RB1 gene, respectively, have already been mentioned. At this point it should be noted that LOH for 22q can be found in approximately 20%–30% of astrocytomas, including well-differentiated and anaplastic tumors [1497, 997, 190], while allelic loss of 13q is rare in well-differentiated astrocytomas [1298].

LOH on chromosome 19q appears to be common to oligodendrogliomas, anaplastic astrocytomas, and glioblastomas. It has been found in approximately 10% of low-grade astrocytomas, more than 40% of anaplastic astrocytomas, and approximately 25% of glioblastomas [3566, 3569, 3570], as well as in 60%–80% of oligodendrogliomas and 30%–60% of oligoastrocytomas [2756, 3570, 2800]. Thus allelic loss of 19q seems to be an early event in oligodendrogliomas and in mixed gliomas, in contrast to the findings in astrocytic tumors, in which the LOH for 19q is significantly associated with anaplasia [3569]. A single tumor suppressor gene on 19q is probably involved in oligodendroglioma formation and in progression towards anaplasia in astrocytomas. This putative gene has been mapped to band 19q13.3, probably in a region of 425 kb between D19S219 and D19S112 [3753].

In oligodendrogliomas, LOH for 19q is frequently closely associated with allelic deletions of the short arm of chromosome 1 [2756, 1776]. LOH for chromosome 1p has been described in 67% of oligodendrogliomas and in 19% of mixed gliomas [2756]. These results suggest that a putative tumor suppressor gene, located on chromosome 1p, is involved in oligodendroglioma tumorigenesis in conjunction with the one suspected on 19p.

In agreement with findings in malignant astrocytic tumors, anaplastic oligodendrogliomas and oligoastrocytomas frequently show LOH on 9p and 10 and epidermal growth factor receptor (EGFR) gene amplification [2756], suggesting common pathways leading to malignancy.

In less than 10% of oligodendrogliomas and in 30% of oligoastrocytomas, allelic loss on 17p has been shown without detectable p53 gene mutations [2756]. Interestingly, in the study carried out by Reifenberger et al. [2756], LOH on 7p in oligoastrocytomas occurred only in patients without LOH on 19q and 1p.

Loss of heterozygosity on chromosome 17p was also observed in about one third of astrocytic gliomas of all degrees of anaplasia (excluding pilocytic astrocytomas), suggesting an early involvement in tumorigenesis [1498, 996, 947]. As mentioned above, p53 gene is located on 17p, and, in fact, p53 gene mutations can be detected in over 60% of astrocytic tumors showing allelic loss on 17p [3565, 998]. However, the absence of p53 gene mutations in at least 30% of gliomas with LOH on 17p suggests the existence of a second tumor suppressor gene on the short arm of that chromosome [947, 2962]. Pilocytic astrocytomas generally do not show deletions on 17p [3567, 2735], whereas deletions on the long arm of chromosome 17 have been detected in one NF1 patient and in three out of 19 sporadic cases [3567]. From these observations, an involvement of NF1 gene in the origin of pilocytic astrocytomas has been hypothesized [3567]. Abnormalities of chromosome 17 have also been reported in ependymomas [3323], which generally show a cytogenetic pattern similar to that found in gliomas (partial trisomy of 7, deletions in 10, loss of 22) [2770, 1169, 3323, 1170, 3648, 3646]. These changes, represented by translocations onto 17p or chromosome 17 loss, were different from abnormalities usually detected in astrocytomas and medulloblastomas.

Chromosomal abnormalities found in medulloblastomas are different from those described in malignant gliomas. Structural changes, such as isochromosome 17q (resulting in loss of one copy of 17p), translocations (8;11), unbalanced translocations of 20q13, and deletions of 6q, 11, and 16q are more common than gain or losses of whole chromosomes [250, 1169, 422]. In agreement with cytogenetic data, molecular genetic studies in medulloblastomas [2709, 3423, 29, 170] have demonstrated LOH on 17p in approximately 30% of tumors, on 6q in 15%, and on 16q in approximately 25% of cases. Loss of alleles on 17p is not associated with p53 mutations, in agreement with the existence of a different tumor suppressor gene on the short arm of chromosome 17 involved in the tumorigenesis of medulloblastomas [233]. A correlation between LOH for 17p and shortened survival period in medulloblastomas has been found by Batra et al. [170].

A recent study was designed to identify allelic loss on 9q in medulloblastomas, starting from observations that patients with the nevoid basal cell carcinoma syndrome (Gorlin syndrome or NBCCS) have increased risk for medulloblastoma and that the gene for Gorlin syndrome has been localized to bands 9q22.3-q31 [3079]. As expected, LOH for 9q22.3-q31 was found in NBCCS medulloblastomas, but also in three out of six patients with sporadic desmoplastic medulloblastomas. In contrast, LOH was not observed in any of 11 other sporadic, nondesmoplastic medulloblastomas. These results are consistent with the existence of a tumor suppressor gene on chromosome 9q involved in the development of at least some desmoplastic medulloblastomas [3079].

Double minute chromosomes occur in approximately 30% of malignant gliomas [249]. Since double minutes are thought to be an expression of gene amplification, many efforts have been addressed to the detection of amplified oncogenes in gliomas. The gene most frequently amplified in malignant gliomas is *erbB1*, coding EGFR [1954, 3711, 994]. EGFR belongs to a group of products of oncogenes that have phosphotyrosine kinase activity. There is evidence that this activity is crucial in the mechanisms of neoplastic transformation involving numerous oncogenes [1435, 1436, 258]. In response to binding with EGF, the receptor is capable of autophosphoryla-

tion on tyrosine residues and of analogous phosphorylation of numerous other proteins, activating a cascade of biochemical events which transmit a mitogenic signal and induce cell proliferation [1435, 605, 432]. Approximately 40% of malignant gliomas – almost exclusively glioblastomas – show EGFR amplification [3711, 808, 20], and over 80% of tumors with amplification contain double minutes [247]. Moreover, a strong correlation between amplification of the gene and increased expression of EGFR has been shown, whereby *erbB1* is amplified in all tumors showing overexpression of the receptor [3711].

In several malignant gliomas EGFR is not only amplified, but also shows nonrandom deletions of the gene involving either the extracellular or the intracellular domain of the receptor [1431, 2079, 809, 3712]. Some mutations lead to loss of the EGF-binding ability, but mutated receptors acquire constitutive tyrosine kinase activity [809]. Therefore, in some malignant gliomas there is overproduction of a truncated receptor, capable of autophosphorylation in the absence of EGF. However, the in vivo significance of these rearrangements and their possible relation with other characteristics of glioblastomas remain unclarified. Moreover, despite much evidence which indicates a key role for EGFR gene amplification in malignant gliomas, data about the correlation of this amplification and prognosis in malignant glioma patients are contradictory [248, 1438, 758, 1900, 2640, 3568, 3045].

There is a striking association in glioblastomas between EGFR gene amplification and LOH on chromosome 10, whereas tumors displaying this association generally do not show LOH on 17p or p53 mutations [3565, 3568, 1900, 2736, 3616a]. The observation that EGFR gene amplification always occurs in patients showing LOH of chromosome 10 has suggested that such amplification probably follows gene loss on 10 [3564]. It is not clear whether EGFR overexpression needs inactivation of chromosome 10 to become oncogenic or whether EGFR gene amplification is a consequence of genomic instability produced by loss of function of some chromosome 10 genes [2013].

In a glioblastoma cell line, a new gene located on chromosome 12 called *gli* has been identified [1686]. It has been shown to be amplified over ten times in two of 45 glioblastomas [248].

In a small number of malignant gliomas or glioma cell lines, amplifications for *N-myc* [1031, 3711, 984, 1437] and *c-myc* [830, 3456, 1227a, 1861, 2736] have been observed. Amplification for *N-myc* and *c-myc* was found in a few medulloblastomas and cerebellar PNET [2433, 2856, 123], whereas amplification of *myc* genes seems to be a relatively common feature of medulloblastoma cell lines [251, 3615]. *N-myc* belongs to the family of *myc* proto-oncogenes which is thought to be capable of modulating genetic expression and cellular proliferation by binding to DNA, even in normal cells [840]. Also in the nervous system, relationships between *myc* and proliferative and differentiation processes have been described many times. In the immature brain, *N-myc* is expressed at high levels [3219, 1150], but during maturation, simultaneous with differentiative processes, the levels of transcription of *N-myc* decrease to those characteristic of the adult [3052]. The expression of the *myc* genes is furthermore induced by the mitogenic effect of different growth factors [840, 1436], while it is repressed as a consequence of the cellular differentiation and of the loss of the proliferative potential [3052].

Amplification of *N-myc* is particularly important in childhood neuroblastomas, where it is a more reliable indicator of a poor prognosis than classical morphological

criteria [342, 3095]. This gene, which has a limited homology with the *c-myc* oncogene, is present in single copies in normal adult cells, while in neuroblastoma cells it is possible to identify up to hundreds of thousands of copies. In 24 out of 63 (38%) neuroblastomas studied, *N-myc* was amplified from three to 300 times [343]. Moreover, a significant correlation between the aggressiveness and prognosis of neuroblastoma and the level of amplification of *N-myc* was demonstrated, in the sense that amplification is frequently associated with more undifferentiated tumors and a worse prognosis. There is a significant correlation both with the stage of the disease and with the histological features of malignancy [3113, 3470].

Expression or amplification of different oncogenes has been detected in some glioma biopsies (*v-fos*, *n-ras*, *met*) [984, 1051, 2510, 1861, 3725] and in several glioma cell lines (*c-mil/raf1*, *neu*, *n-ras*) [1834, 1051]. The significance of these findings is unknown and further studies are needed to correlate the oncogenic expression with histological and clinicopathological features of glial tumors.

Important findings arose from studies concerning the expression of PDGF and PDGF receptor genes in gliomas. The first important finding is that the PDGF B chain is encoded by the *c-sis* proto-oncogene, the cellular homologue of the oncogene *v-sis* of the simian sarcoma virus (SSV) [755, 3617]. SSV, when injected intracranially in a newborn marmoset, may induce gliomas, and its oncogenic action is mediated by a growth factor that binds to the PDGF receptor [2806]. Moreover, it has been reported that many human malignant glioma cell lines express PDGF genes and, in some cases, PDGF receptors as well [2440]. Different studies have demonstrated coexpression of PDGF genes and of PDGF receptors in vivo in biopsies of human astrocytic gliomas [1304, 2182, 2179, 1305, 1186]. These results suggest the presence of an autocrine growth loop contributing to neoplastic proliferation in astrocytic gliomas of all degrees of malignancy. The expression of PDGF A and B chains is detectable in all astrocytic tumors, though is probably higher in glioblastomas. PDGF- $\alpha$  receptor is expressed in tumors of all grades, whereas PDGF- $\beta$  receptor is expressed mainly in malignant tumors [2179, 1305, 1186]. Furthermore, few astrocytomas show amplification of the gene encoding PDGF- $\alpha$  receptor [2736], in conjunction with deletion of an exon-coding part of the extracellular domain of the receptor [1804].

Evidence for PDGF- $\beta$  receptor expression by vessel cells of human gliomas has been reported [1113, 2182, 2179, 1305]. This finding may be extremely important in understanding the pathogenetic mechanisms of endothelial hyperplasia in malignant gliomas. A paracrine growth stimulation mechanism, involving PDGF produced by glioma cells and the receptor expressed by endothelial cells, may be active. However, it has been reported that hyperplastic endothelial cells of glioblastomas may also express PDGF B chain mRNA [1304, 2182, 1305]. This suggests the possibility of an autocrine loop as well [1304]. An autocrine mechanism may account for the pseudotumoral growth of endothelium and for sarcomatous proliferations that originate from hyperplastic vessels of glioblastomas, giving rise to mixed tumors such as gliosarcomas.

An autocrine loop involving PDGF B chain and PDGF- $\beta$  receptor has also been demonstrated in meningiomas [1626, 2183, 265, 3608, 895, 2180]. The use of suramin, an inhibitor of different growth factors including PDGF, has been proposed as a treatment for controlling meningioma proliferation in patients with inoperable meningiomas [3089].

Other growth factors have been investigated in relation to brain tumors. Transforming growth factor- $\beta$  1 (TGF $\beta$ -1) and TGF $\beta$ -2 are expressed in gliomas [2939, 1539, 928, 1391, 2373] and meningiomas [2441, 1547], and have been implicated in control of different aspects of glioma pathogenesis, including control of cell growth, invasiveness and migration, angiogenesis, and immunomodulation [2854, 2184, 1484, 2248].

Neoplastic astrocytes express basic fibroblast growth factor (bFGF) [3374, 3771] and two receptors for this growth factor, FGR1 and FGR2 [2334, 3482]; an autocrine growth loop can thus be hypothesized [2334].

Finally, different studies have suggested the possible involvement of insulin-like growth factor 1 (IGF-1) and its receptor in the control of glioma cell growth [1096, 76, 2028, , 3460, 2767].

Recently, a possible role of homeobox genes (see Sect. 1.5) in processes of neoplastic transformation has been suggested in different tumor types and documented in leukemia [1883]. Expression of *PAX5*, *PAX6*, *EN1*, and *EN2* has been demonstrated in medulloblastomas [1766]; the expression of *PAX5* is of particular interest, because this gene is not expressed in normal cerebellum, suggesting a deregulated expression in medulloblastomas [1766]. Moreover, the expression of genes of different HOX clusters has been observed in malignant gliomas and in medulloblastomas [721].

## 2.2

### Familial Incidence of Tumors

The familial occurrence of medulloblastoma is known. Up to 1986, 21 cases had been reported [3437]. Eight involved monozygotic twins, nine occurred in brothers, and eight occurred in brothers of cases with other tumors. Of all these cases, two were congenital. There are many reports in the literature of familial astrocytomas and glioblastomas [3076, 2985, 2931, 1316, 1890, 3545, 2011]. In some cases there was concordance for site [2985] and for multicentricity [1316]. Very peculiar is the case in which two brothers, 2 and 5 years old, simultaneously manifested a glioblastoma [786].

It remains controversial whether the risk of brain tumors in the relatives of patients bearing brain tumors is increased [506, 867] or not [2683, 1357, 1116]. There have been discussions on whether the probability of occurrence of cerebral tumors was equal [2683, 1357] or greater [506] in the relatives of patients with tumors, but the role of heredity has not been recognized [867].

Retinoblastoma is hereditary, and certain hereditary tumor syndromes are known to carry an increased risk of CNS tumors. These include neurofibromatosis, Bourneville's disease, Li-Fraumeni syndrome, ataxia telangiectasia, Gorlin syndrome, and Turcot's syndrome (see Chap. 22).

## 2.3

### Congenital Tumors

Tumors appearing within 60 days from birth used to be considered congenital [94], but opinions then diverged on this point. Other authors have, in fact, considered as



“certainly congenital” tumors producing symptoms at birth, as “probably congenital” tumors producing symptoms in the first week of life, and as “possibly congenital” tumors producing symptoms in the first month [3259]. This subdivision was later reviewed, and the term of “possibly congenital” tumor was extended to those producing symptoms within the first 2 months of life [3587]. The limits of the three categories were later fixed at 6 weeks, 6 months, and 12 months, respectively [816].

Within the first 2 months of life, cerebral tumors are very rare and represent a proportion which is not greater than 1.5% of all cerebral tumors of infancy. Up to the end of 1984, 115 cases had been described, 12 of which were “probable” and 66 “possible” congenital tumors [1555]. An additional six were found incidentally at autopsy [3587]. In the distribution of oncotypes, teratomas figured in first place (36.5%), followed by medulloblastomas, astrocytomas, and plexus papillomas. Supratentorial localizations prevail, and, importantly, the majority of teratomas are not of the pineal region but of the third and lateral ventricles. Still, note worthy is the numeric importance of mesenchymal tumors, excluding meningiomas. In a series of 17 patients [1554], a prevalence of supratentorial tumors was found, but only two teratomas were observed. Following teratomas, medulloblastomas were the most frequent, 13 of 55, in a series of fetal and neonatal tumors [1506]. Up to 1986, 26 examples had been reported [903]; two cases, besides being congenital, were also hereditary [1167].

Twenty-six congenital tumors, representing 11.3% of tumors in the first year of life, were found in a Japanese series [2482]. Teratomas were the most frequent type, whereas astrocytomas were the most frequent form in the first year of life in five Far Eastern countries [2483]. In a series of 100 cases, representing 7.7% of all intracranial tumors of childhood, medulloblastomas were the most frequent. However, in a recent review of 886 cases of tumors of the first years of life, collected from five geographical areas, astrocytomas turned out to be the most frequent tumors, followed by medulloblastomas, ependymomas, etc. [724]. In a series of 93 cases during the first 18 months of life in the United Kingdom, the most frequent tumors were medulloblastoma, ependymoma and astrocytoma. Only one teratoma was found [1813].

## 2.4

### Risk Factors: Epidemiological Data

The source of data relating to risk factors for cerebral tumors in man is twofold, descriptive clinicopathological studies and epidemiological studies [3721]. The former have described the association of cerebral tumors with various factors (e.g., individual characteristics, professional and nonprofessional exposures, diseases), while the latter (more often case-control studies) have tried to confirm the significance of the associations previously suggested and to identify others which are still unknown. All the case-control studies have shown a certain number of methodological problems, which may explain the contrasting data which often emerge [3074, 1935].

In general, when many risk factors are analyzed simultaneously, a certain number of the observed associations may be purely casual. The choice of controls to compare with cases of cerebral tumor is always a crucial problem. If only healthy controls are used, a potential limit is the so-called selective recall, i.e., a greater anamnestic effort

from relatives of the index case with brain tumor, who are more emotionally motivated than the relatives of the healthy controls, with consequent disparity of information on the risk factors. As a consequence, there would be a need to utilize, apart from healthy controls, which by themselves guarantee a greater generalization of the data obtained, sick controls and, in particular, patients with a noncerebral tumor. Sometimes, however, the utilization of different types of controls may lead to uncertain results: The consumption of barbiturates was found to be increased in mothers of patients with brain tumors, when compared with control mothers of patients with other types of neoplasia, but the difference became much less evident when the comparison was made with mothers of healthy controls [1113]. Another fundamental problem, especially in the study of professional exposure, is how a given exposure is measured; a different measurement of the intensity and of the duration of the exposure to the same risk factor may lead even to opposite and anyway not comparable results. An extremely serious risk is not to measure an exposure which really occurred ("misclassification of exposure"), especially if this occurs in a different manner for tumor cases and controls.

The majority of analytic epidemiological studies on cerebral tumors put different histological types in the same category, even with specific incidence and survival; thus there is very little available data for single categories (e.g., gliomas, medulloblastomas).

#### 2.4.1

##### Family Characteristics

The majority of the familial characteristics investigated in case-control studies of infantile and adult cerebral tumors have not been found to be associated with a significant increase in the risk for cerebral tumor. These characteristics are: congenital diseases [1114], maternal or paternal age at birth of the index case [506, 1114, 2397], the mother's average age of menarche [1114], maternal diseases preceding the birth of the index case [506], type of religion and schooling [2397], and ethnic group [386] of the parents. Equivocal results have emerged for other maternal characteristics, such as a positive history of abortion and complications of delivery [2219, 506] or for epilepsy and "stroke" [1114], while, in the only available study [1114], the association between infantile cerebral tumors and epilepsy in consanguineous brothers and sisters has been found to be statistically significant.

The association between maternal habits and increased risk of infantile cerebral tumors has been found to be negative for the use of contraceptives by the mother before the birth of the index case, tobacco consumption before pregnancy, and use of hormones during pregnancy [1114]. The suspicion that barbiturates employed as medication for epilepsy may cause brain tumors has been a matter of debate. The possibility was raised in a case-control study [1113]. In an investigation on barbiturate exposure during childhood and in utero [1121], an association was found only for barbiturate use during childhood, but it was reduced to insignificance when the history of epilepsy was considered. The use of phenytoin alone or in association with barbiturates during pregnancy has been correlated with infantile CNS tumors [1979]. Also, for drugs with CNS actions, i.e., sedatives and antidepressants, employed dur-

ing pregnancy, the association was uncertain in particular, for neuroblastoma [1773]. A positive association was found for maternal antinausea medication [1721] and for the consumption of food with potential sources of *N*-nitroso compounds, such as variously treated meats, e.g., smoked, pickled [2684].

The importance of parental exposure has been taken into account as risk factors. Paternal exposure to hydrocarbons does not seem to be significant [3770, 2942, 1115, 2397]. Studies [2497, 2397] have not confirmed the original suggestion of a risk connected with the work of the father in the aerospace [2625], cellulose, or wood-pulp industries [1831]. Paternal exposure in the chemical industry [1115, 2397], in the petroleum industry, and in industries involving the use of electromagnetic fields [2397] is not significant. In the last case, however, some doubts remain for peripheral nervous system (PNS) tumors [3279]. The association is negative for maternal exposure to ionizing radiation, while it is equivocal for paternal exposure [2397].

Parental occupations have also been taken into account for risk factors, with wide discrepancies. A case-control study [3678] relying mainly on the Hoar job exposure matrix, revealed a pattern of greatest excess risk for paternal jobs held prior to conception in agriculture, transportation, construction, involving exposure to metals, paints, hydrocarbons, or nitrocompounds, whereas few associations emerged for maternal employment characteristics.

In other studies [1088, 573] no factor was definitely identified.

#### 2.4.2

##### Individual Factors

The order of birth does not represent a risk factor for cerebral tumors in adults [506, 386]. Being the first born and being heavy at birth is positively associated with infantile cerebral tumors, but without statistical significance [1114]. The blood group A has been found to be positively associated with intracranial tumors in males [368] and with gliomas in general [3125], and blood group O with hypophyseal tumors [2187]. By contrast, some authors deny the importance of blood groups [1025, 506]. Religious affiliation and tonsillectomy are not important [1114, 386]. Patients who are immunosuppressed because of renal transplants have a 350-fold greater risk than controls of developing lymphoma, many of which are cerebral [1378].

Various diseases have been reported to be associated with CNS tumors, but for none of these has a thread of significance emerged. This applies to diabetes mellitus [2570, 96] and toxoplasmosis [3094]. The association between breast cancer and meningioma [3076], likely on a hormonal basis, and that between osteosarcoma and hereditary retinoblastoma [5, 762] are, however, significant. In ataxia telangiectasia, extracranial tumors occur more frequently than expected [644], but it is not known whether this disease represents a significant risk for CNS tumors too [1935].

### 2.4.3

#### Multiple Sclerosis

The association between gliomas and multiple sclerosis is not frequent. Up to 1991, no more than 25 cases had been described. The majority of the tumors were astrocytomas/glioblastomas; only two cases were oligodendrogliomas [155, 1076].

In the majority of cases, the tumor has not been clinically diagnosed; in some cases, demyelinating plaques have accidentally been found at autopsy in patients with gliomas. This association has been considered as casual by some [336, 318, 104, 63, 1076, 1], while others considered the tumor as originating from the transformation of reactive glia [2983, 2745]. The finding that tumor and demyelinated areas are contiguous would militate in support of the latter hypothesis [2983, 336, 2745, 622, 2903, 63, 1843], but in many cases this is not observed [2357, 155, 318, 104, 2148, 622]. It is also possible that the growing tumor obliterates the demyelinated areas.

Oligodendrogliomas could originate from the proliferation of oligodendrocytes in the plaques [1447, 2044], but the rarity with which oligodendrogliomas are associated with multiple sclerosis would be inconsistent with the importance of oligodendroglial proliferation in the process of demyelination.

Some of the associated tumors were multiple [2983, 2745, 622]. The hypothesis of a common viral origin has not been confirmed [1572]. The postulated causal association is in contrast with the finding that the number of described associations is lower than that expected on the basis of the prevalence of multiple sclerosis and the tumor mortality [3402]. However, the association in reported cases may not reflect the real frequency of association [1076].

### 2.4.4

#### Virus

There are reports of positivity for viral antigens, for example, SV40, or of DNA or RNA sequences in different tumors, but decisive proof for a viral origin of cerebral tumors is lacking. Sometimes, sequences were left after infections in infancy by human viruses with widespread diffusion [1697].

Malignant gliomas have been occasionally found in patients with acquired immunodeficiency syndrome (AIDS), without a clear correlation to the infections and the modulating immunoincompetence [475]. In contrast, a constant association between Epstein-Barr virus (EPV) and primary CNS lymphomas in immunocompromised patients has been found (see Chap. 23).

### 2.4.5

#### Head Injuries

The appearance of cerebral tumors after head injury has repeatedly been reported to occur. This would directly imply the neoplastic transformation of reactive astrocytes. Despite reports that posttraumatic neuroepithelial tumors are not rare [3060], cases which satisfy the criteria of acceptability are few [3574, 2623, 1769]. These are

[3799]: adequately serious trauma, origin of the tumor at the site of trauma, absence of CNS diseases before injury, reasonable latency period between trauma and onset of the tumor, histological demonstration, and direct continuity with the traumatic scar [2099]. In a recent case [3466], as in others previously reported [902, 3704], trauma was due to a splinter from a bomb. On the whole, it can be said that there does not seem to be a positive association between trauma and primitive cerebral tumors [506, 71], even considering only gliomas [386, 2687], unless the head injury has been severe [1356, 1418].

By contrast, the association between head injury and the development of meningiomas suggested by single reports [2772, 3599, 3383] has subsequently been confirmed in case-control studies both in females [2683] and in males [2686, 2687]. A limiting factor in these studies was, however, represented by the impossibility of evaluating the etiogenetic role of the head injury separately from that of exposure to X-rays, as radiography was employed in the same patients to evaluate the consequences of the trauma. A complete review of the subject is available [2305].

Experimental data concerning the putative relationship between trauma and the development of brain tumors until now have given contrasting results. In transplantably by ethylnitrosurea (ENU) treated rats injured by an intracranial needle-trauma at 12 days of age, no effect on the number and location of tumors was observed [2240]. In another study in similar rats, a greater percentage of gliomas was found on the traumatized side [2306]. In our experience with the same rats, trauma seems to act as a factor anticipating the appearance of gliomas [3029].

#### 2.4.6

##### Irradiation

Data on the risk of development of cerebral tumors after prenatal exposure to X-rays for diagnostic use are contrasting: The 60% increased risk reported by McMahon in 1962 [2219] has not subsequently been confirmed [506].

Postnatal exposure (skull and dental X-radiography) has been found to be positively associated with the development of meningiomas [2686] in both females [2683] and males [2686]. Repeated dental X-radiography, especially before 1950 when this procedure entailed exposure to very high radiation doses, have been thought to increase the incidence only of tentorial or infratentorial tumors.

There are many reports indicating exposure to X-rays as a treatment for tinea capitis as a risk factor in children. Worldwide, 250 000 children underwent the Adamson-Kienböck irradiation technique for tinea capitis during the years 1910–1959, i.e., a radiation dose of 70–200 rad [3647]. Evidence indicates a relationship between small doses and tumors such as meningiomas [2290, 2865] and gliomas [3174, 2825]. A glioblastoma associated with multiple meningiomas, a malignant cerebellar astrocytoma, and a diffuse astrocytoma have been described in patients many years after exposure to low-dose irradiation [3247]. The induction of meningiomas by irradiation is now well established, and radiation-induced meningioma seems to be a recognizable entity. A supplementary case has been reported [2562].

There are many reports of second CNS tumors arising after radiotherapy for intracranial tumors. They are usually meningiomas [2093, 3245, 2865, 1811, 2336,

3246] and sarcomas [2448, 113, 213, 3436, 1811, 3384]. Gliomas are much less frequent; 24 cases had been reported up to 1985 [1991], but others have been published subsequently [1560, 2057, 3491, 1424, 927, 3050, 732, 2547, 1692, 3140, 461, 2936].

A recent analysis of possible radiation-induced tumors includes 89 gliomas, 36 sarcomas, and four gliosarcomas [1602]. Seven additional gliosarcomas have been observed [2618], caused by irradiation of glioblastoma multiforme. The problem of "secondary" gliosarcomas is very interesting, because these tumors may also develop spontaneously and no pathologic difference has been found between them and the spontaneous ones [2618]; whether therapeutic irradiation given for glioblastomas induces sarcomatous transformation is therefore still a matter of debate. However, irradiated glioblastomas show changes in their vasculature that, at a temporal distance from irradiation, acquire aspects close to those of gliosarcomas [3031].

Out of 305 patients treated with megavoltage radiation therapy for pituitary adenoma, four developed gliomas. The latter arose within the previous radiation fields, with a latency period of 8–15 years after radiation. The risk of malignant brain tumor was 16 times greater for the treated patients than for general population [3469] (for pathogenetic considerations, see Chap. 9). In the reported cases, the dose varied between 150 and 6000 rad. The irradiation was usually given for infantile tumors, and the majority of published cases were therefore in the first three decades of life. Irradiated primary tumors were mostly medulloblastomas, craniopharyngiomas, and acute lymphoblastic leukemias.

Criteria are available to determine whether a correlation between radiotherapy for a first neoplasm and the development of a second tumor exists: (a) both tumors have to be histologically verified; (b) the second tumor has to develop in the irradiated area; (c) there must not be similarities of site and histological appearance between the two tumors; (d) the latency period has to be sufficiently long to exclude the presence of the second tumor at the time of irradiation. The role played by radiotherapy in the induction of the second neoplasm is very controversial, even though the cases reported in the literature and experiments in monkeys are in favor of a causal role of radiotherapy [1635, 3457, 1274, 1791]. Our knowledge of radiobiology is not in contrast with this hypothesis. Theoretically, the risk of a second intracerebral neoplasm after therapeutic irradiation is more than 100 times greater than in controls [461].

#### 2.4.7

##### Nonprofessional Exogenous Exposures

Smoking has never been found to be a potential risk factor [506, 2683, 2365, 1357]; however, in the wide Canadian case-control study published in 1987 [386], the use of cigarettes without filter was found to be significant.

The positive association with the use of hair dyes or hair sprays recently reported [386] must be reevaluated, because many of these products, being oxidants, are well known as potent mutagens [3536] and have been found [3175] to be positively associated with extraneural tumors such as, for example, mammary carcinoma.

The exposure to *N*-nitroso compounds and their precursors or modulators in food has been actively investigated, in the light of experimental data on the very well known carcinogenic potential of such substances on nervous tissue, but the results

have often been contrasting or even incongruent. High risks for gliomas have been found for the consumption of salted, smoked, and pickled fish [386]. The latter represents an important source of nitrosoamines and perhaps of nitrites. The consumption of other meat products, also important sources of nitrites, was found to be positively associated with the risk of infantile and juvenile tumors [2684]. In the Los Angeles area, it was found to be a significant risk factor for meningiomas in females [2683], but not in males [2686]. The consumption of alcohol is not significant in some series [506, 2365, 1357], while in others [386] wine consumption represents a risk factor for gliomas. Analogous discrepancies have been found for beer consumption [386, 1418], which contains higher concentrations of nitrosoamines than wine. From a case-control study [386], a protective role of fruit consumption has emerged. This could be in relationship to the elevated content of vitamins C and E, which are known to be inhibitors of the formation of *N*-nitroso compounds from nitrites and other precursors [2284, 3618].

The use of oral contraceptives has not been found to be associated with a risk for pituitary adenomas in American women [70].

Two cases of children with high urinary levels of lead who subsequently developed an astrocytoma were reported [3088]. Even if anecdotal, this datum is not to be undervalued in the light of the demonstrated experimental inducibility of gliomas in rat with diets rich in lead citrate [2521].

Different nonprofessional exposures have been examined [1114] in a case-control study in children. Positive associations have been found with living on a farm and a history of contact with farm animals. Some associations, even if they do not achieve statistical significance, have been emphasized because of their potential biological significance, for example, that with insecticides and sick pets. This association was subsequently denied [1418]. It has been showed that folate, early multivitamin use, and iron supplements by the mother during pregnancy protected their children against brain PNET, including medulloblastoma [385].

#### 2.4.8

##### Professional Exogenous Exposures

The increased risk for cerebral tumors in rubber industry workers is controversial. Equal numbers of reports confirm [2089, 2299, 386] and deny [2220, 2212] it. The same uncertainties remain for workers in the petrochemical [3428, 3620, 1901, 111, 3426], pharmaceutical [3425, 2212], and textile [2365, 2212] industries, for chemical workers [2490, 386], for glassmakers [832, 3695, 2212], and for subjects exposed to vinyl chloride [3621, 386]. Some studies, however, indicate an excess mortality for cerebral tumors in workers in the petrochemical industries [2425, 34].

An excess mortality from cerebral tumors in various categories of subjects exposed to electromagnetic (nonionizing) radiation, such as electrical and electronic engineers, electricians, telephone and telegraph line operators [2685, 2088, 2265, 1963, 2959], has been reported. Different studies have reported a shorter latency between the initiation of the exposure and the onset of tumors than that known for other forms of professional carcinogenesis for example, that due to asbestos [3115, 3650], it has been hypothesized [1963] that the oncogenic action of electromagnetic

radiation might occur through a mechanism of facilitation more than initiation of the neoplastic growth. This hypothesis may be in agreement with the finding in extracerebral experimental tumors of a “promoting” effect of such radiation [3322, 1137], even if, for now, the only actions demonstrated on the nervous tissue concern the possibility of inducing gliosis [1667] or modifying the bond with calcium ions [14]. Some studies, especially case-control ones, however, denied [2491, 2212] or attenuated [3427] the carcinogenic risk for the CNS of electromagnetic radiation. In particular, the increased risk of gliomas in the electronic industry involves categories both exposed and nonexposed to electromagnetic radiations [3427]. The hypothesis, therefore, is that the increased risk of cerebral tumors was due, at least in part, to the exposure to various chemical products used in the electronic industry, especially solvents (e.g., trichloroethane, tri- and tetrachloroethylene), which may induce gliotic phenomena in cerebral tissue [2844].

The increased risk of gliomas in agricultural workers, originally suggested in a descriptive epidemiological study [348], is controversial [2365, 386, 2212, 2366, 2277]. A significant increase has been found in agricultural workers who used fungicides and insecticides, but not herbicides and fertilizers [2366]. Some of the fungicides commonly added to copper sulfate compounds used in vineyards contain alkyl ureas, which are the precursors of the *N*-nitroso-alkyl ureas.

An increased incidence of gliomas has been hypothesized in various health workers. The risk would seem significant for pathologists [1241] and anatomists [3329], perhaps following exposure to formaldehyde or other chemical agents, and for dentists and their assistants [23] who handle mercury and various metal amalgams.

Both descriptive and analytical studies agree in attributing an increased risk of gliomas to welders [832, 433, 2212], while there are single reports for categories with exposures similar to those of welders (e.g., plumbers, millers) [2212]. A recent case-control study on occupational risks in Sweden [2212] has suggested, for the first time, an increased risk of gliomas in ceramic, porcelain, and brick workers.

A risk of cerebral tumors has been found to be elevated even in attorneys and lawyers [771, 2212]. It is possible that these categories are prone to a greater diagnostic accuracy.

#### 2.4.9

##### Multiple Tumors

One of the arguments supporting the theory of the multicentric growth of cerebral tumors, particularly of gliomas, is the occurrence of diffuse and multiple gliomas. From diffuse gliomas, mostly astrocytomas and oligodendrogliomas, gliomas with multicentric growth and diffuse glioblastosis, also called diffuse spongioblastosis [3799], must be kept separate. Diffuse glioblastosis is a rare form which especially affects the young, in the brainstem or in the hemispheric white matter, and has a recognized dysontogenetic origin. Multicentric gliomas are tumors in which growth centers may be very distant from each other. According to Courville (1936) [582] 10% of glioblastomas and 6% of astrocytomas are multiple.

The majority of multiple gliomas are found only in one hemisphere, but they can also be symmetrically distributed and often have similar dimensions. Glioblastoma



prevails, but other histological types are also represented. Although rare, contemporaneous cerebral and cerebellar locations have been described [3799, 2904]. Periodically, cases of multiple gliomas are reported in the literature [3385, 470, 154, 2285] with an incidence varying from 2.5% to 8.75%.

The main problem concerning multiple gliomas is whether they actually represent true multicentric foci [582, 294] or are expressions of metastases within the nervous system. In 1962, Solitare [3258], critically reviewing the problem in relation to a cerebral-cerebellar glioma, warned against the possibility that multiple foci are not distinct foci but appear so because of insufficient examination of the intervening nervous tissue, as others have [3799, 172].

Nevertheless, it has recently been reiterated that the pathogenesis of multiple gliomas may be an expression of a true formation of multiple primary growths, of contemporaneous disturbance of development leading to coordinated tumors [2514], or of metastatic disseminations along CSF pathways [378]. Obviously, the entire brain must be examined in order to accept a tumor as multicentric. It has, in fact, been demonstrated that some apparently multicentric glioblastomatous foci are connected by a diffuse astrocytomatous proliferation. This case might represent a multicentric malignant transformation of a diffuse astrocytoma [2990]. Some multicentric growths on CT scan may be found to belong to this category after histological examination. True multicentric gliomas occur in 8% of our autopsy series.

Multiple tumors of diverse nature are considered separately, because the pathogenetic problem is different. They may belong to hamartoblastomatosis, such as von Recklinghausen's disease, in which multiple neurinomas, meningiomas or astrocytomas are associated. In addition, combinations of mesodermal tumors, such as multiple meningiomas, or of mesodermal and neuroectodermal tumors may occur. Not infrequent is the association between meningiomas and gliomas, usually astrocytomas and glioblastomas, but also oligodendrogliomas. In all, 18 cases from the literature plus a personal one of meningiomas associated with gliomas of various type were reported [813]. The number amounted to 25 some years later [909]. Single cases are periodically reported in the literature [3328, 92]. The association of glioma and meningioma has been found to be the most frequent one [67, 699].

Other associations found were between glioma and hemangioblastoma, craniopharyngioma and meningioma, meningioma and neurinoma [699], and craniopharyngioma and astrocytoma [443], and craniopharyngioma and pinealoma [1276]. The association astrocytoma-neurinoma is rare [584, 1297, 405]. Sarcomas not infrequently appear in association with other tumors [2186], and this involves the more general problem of mixed sarcomatous tumors. Also rare is the association between pituitary adenomas, gliomas, and meningiomas. The association between primary lymphoma of the brain and meningioma has been reported only once [3223]. From the pathogenetic point of view, it is important to note that in the majority of cases, the tumors belong to anatomically adjacent areas and, therefore, stand in probable causal relationship [405].

## Experimental Tumors

### 3.1

#### Chemical Carcinogenesis

##### 3.1.1

##### Topically Acting Carcinogens

The experimental induction of cerebral tumors was initially accomplished at the site of application of the carcinogens. Polycyclic aromatic hydrocarbons such as 20-methylcholantrene [3788], 1,2,5,6-dibenzanthracene [93], and 3,4-benzopyrene [3789] were the ones most used, by means of pellets implanted in the brain. The histological type of tumor obtained depended on the site of implantation [3787], e.g., ependymomas in the ventricles, glioblastomas and oligodendrogliomas in the white matter, medulloblastomas in the cerebellum. It was clear that the subependymal zone could play an important part in the development of these tumors [1382].

##### 3.1.2

##### Resorptive Carcinogens

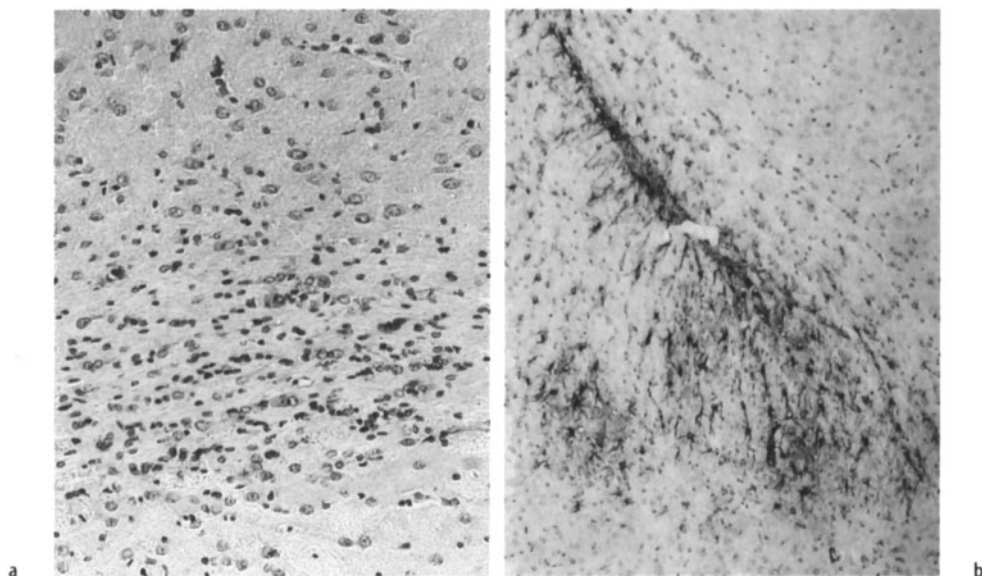
A tumor was not induced at the site of application of the carcinogen, but in different organs towards which it shows a specific tropism. The first studies were based on the observation of occasional tumors in rats, produced by 2-acetylaminofluorene [3526, 1355, 3357], 8-orthohydroxycholesterol [1354], and 2,7-fluorenbisacetamide [3238]. Subsequently, a systemic induction was obtained, after the demonstration of the hepatic carcinogenic activity of nitrosamine [2065], with compounds belonging to the nitrosourea group. Numerous nitrosourea derivatives have been studied [766]. Nitrosamides appeared to have a strong neurotropism.

Two compounds in particular have been found to be ideal for developing an experimental model, methylnitrosourea (MNU) and ethylnitrosourea (ENU). Tumors could be produced in the adult animal, in the neonate, and transplacentally, with in every case a relationship between administration route, dose of carcinogen, and latency period being demonstrated (see Table 3.1). The tumors seen are mostly gliomas, arising mainly from periventricular areas and from the hemispheric white matter [3627, 1738, 766], and neurinomas of the fifth nerve or of the spinal roots [1176, 3355], which are morphologically similar to spontaneous tumors in humans and animals. More tumors may develop in the same animal, and tumors in different phases of development may be found at the same time in the same animal.

**Table 3.1.** Induction of tumors in the rat

Carcinogen	Animal	Administration		Site	Dose (mg/kg)	Latency period (days)
		Route	Day of pregnancy			
<i>Prenatal induction (transplacental)</i>						
Ethylnitrosourea	Rat	Intravenous	15–17	SNC	80	150
				SNP	5	250
Ethylnitroso-biuret	Rat	Oral	15	SNC	100	190–330
				SNP		
1,2-Diethylhydrazine	Rat	Intravenous	15	SNC	50–150	126–560
				SNP	5–10	560
Azoethane	Rat	Inhalational	15	SNC	300	220
				SNP	600	126–480
Azoxyethane	Rat	Intravenous	15	SNC	50	142–300
				SNP		
Ethyltriazenes	Rat	Intravenous	15	SNC	110	350
				SNP	55	450
1,2-Dimethylhydrazine	Ineffective					
Azoxymethane						
Methyltriazene	Ineffective					
<i>Neonatal induction</i>						
Ethylnitrosourea	Rat	Intravenous		SNC		180–600
		Subcutaneous		SNP	5–80	
		Intracerebral			1st–30th day	
Butylnitrosourea	Rat	Subcutaneous		SNC		130–180
				SNP	120, 1st day	
Ethyltriazenes	Rat	Subcutaneous		SNC		190–250
				SNP	50, 1st day	
Methylnitrosourea	Ineffective					
Ethyltriazenes						
<i>Induction in the adult animal</i>						
Methylnitrosourea	Rat	Intravenous		SNC		
	Rabbit	Oral		SNP	5 mg/g	280–500
					per week	
	Dog	Intraperitoneal				
		Intravenous		SNC	3 mg/g	
					per week	450
Dimethylnitrosourea	Rat	Oral		SNP	40 mg/kg	210
					per week	
Trimethylnitrosourea	Rat	Oral		SNP	3 mg/g	450
					per day	
		Intravenous		SNC	25 mg/g	
					per week	410
Ethyltriazenes	Rat	Subcutaneous		SNP	50 mg/g	
					per week	250
Ethylnitrosourea	Ineffective					

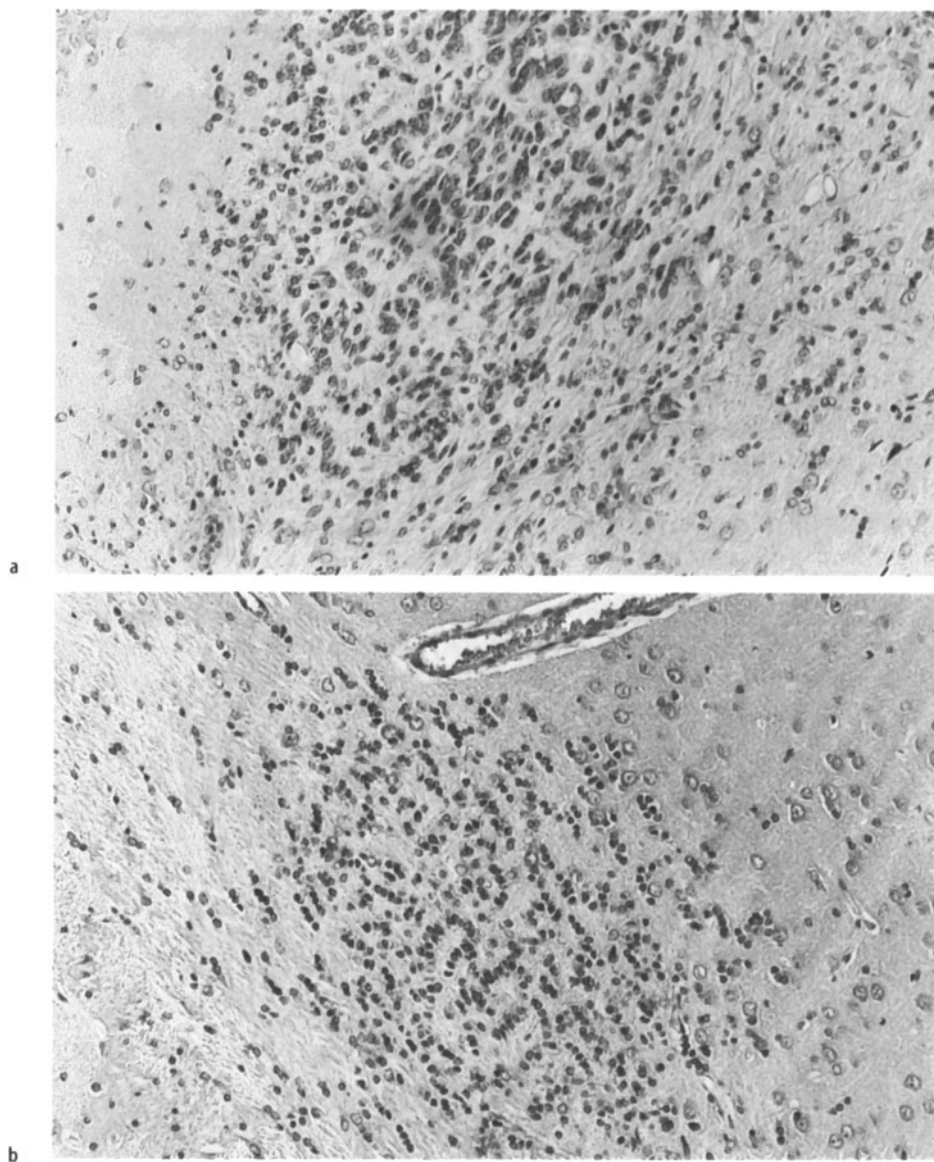
The frequency of tumors and multiple tumors is dose-dependent.



**Fig. 3.1a,b.** Rat transplacentally treated with ethylnitrosourea (ENU). **a** Early neoplastic proliferation (ENP) in the white matter. H&E,  $\times 200$ . **b** ENP, intense glial fibrillary acidic protein (GFAP) staining of reactive astrocytes. PAP-DAB,  $\times 200$ . (From [2175])

MNU is active in the adult animal, while ENU is active in the neonate and transplacentally. MNU repeatedly administered by the intravenous route produces gliomas in the brain and in the spinal cord and neurinomas of the gasserian ganglion within 280–500 days.

Very important and widely used is the transplacental model with ENU. A single i.v. dose of 20 mg/kg in the rat on the 17th day of gestation causes cerebral tumors in 90% of the offspring. Increasing the dose of ENU increases the number of tumors per rat and decreases the latency period [766]. The period of clinical latency, i.e., between birth and the first appearance of symptoms, is 5–6 months [2739, 313]. At this age, however, neoplastic lesions at different stages of development are found; if animals are systematically studied starting from birth, the first tumors are found at the second month of extrauterine (e.u.) life in the periventricular white matter [3010, 1869], known as early neoplastic proliferations (ENP; Fig. 3.1a). Histologically, they are not very well defined [1699, 3354, 1866]. Astrocytes and oligodendrocytes are present, apart from cells of uncertain nature [3010]. The abundance of reactive astrocytes in these lesions is striking [3012, 2175] (Fig. 3.1b). Between the second and the third month of e.u. life, microtumors of a diameter between 300 and 500  $\mu\text{m}$ , with higher cell density, frequent mitoses, and proliferation centers of densely packed cells, develop from these lesions [1738]. Microtumors continue to appear between the fourth and the fifth month (Fig. 3.2a), while oligodendroglial foci begin to be evident in the cortex and in the white matter between the third and sixth month (Fig. 3.2b). Isomorphous tumors develop from microtumors and become polymorphous. Adult isomorphous oligodendrogliomas (Fig. 3.3) develop from oligodendro-



**Fig. 3.2a,b.** Rat transplacentally treated with ethylnitrosourea (ENU). **a** Microtumor. H&E,  $\times 200$ . **b** Oligodendroglial focus between white matter and cortex. H&E,  $\times 200$

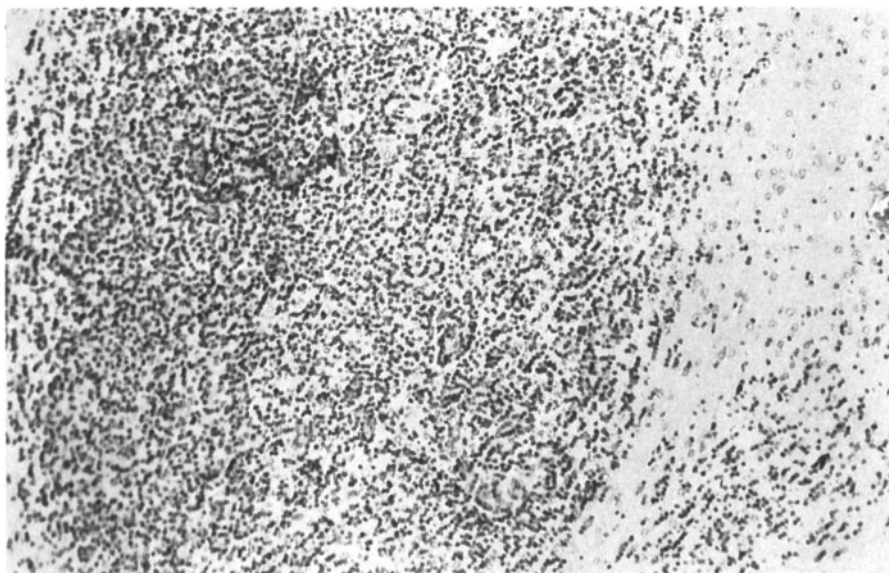


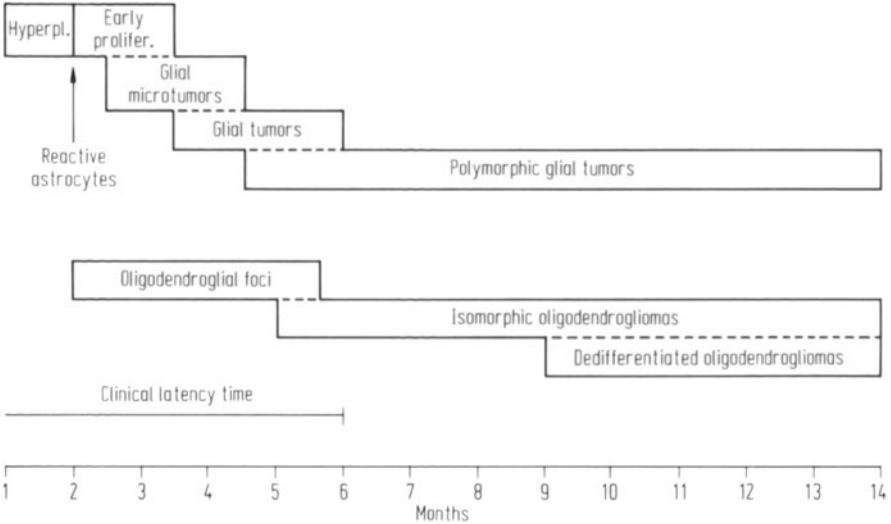
Fig. 3.3. Rat transplacentally treated with ethylnitrosourea (ENU), isomorphic oligodendroglioma. (From [3034]) H&E,  $\times 150$

glial foci and may become polymorphous. Malignant growth is reached at the stage of microtumors [3627]. The entire temporal sequence is reported in Fig. 3.4.

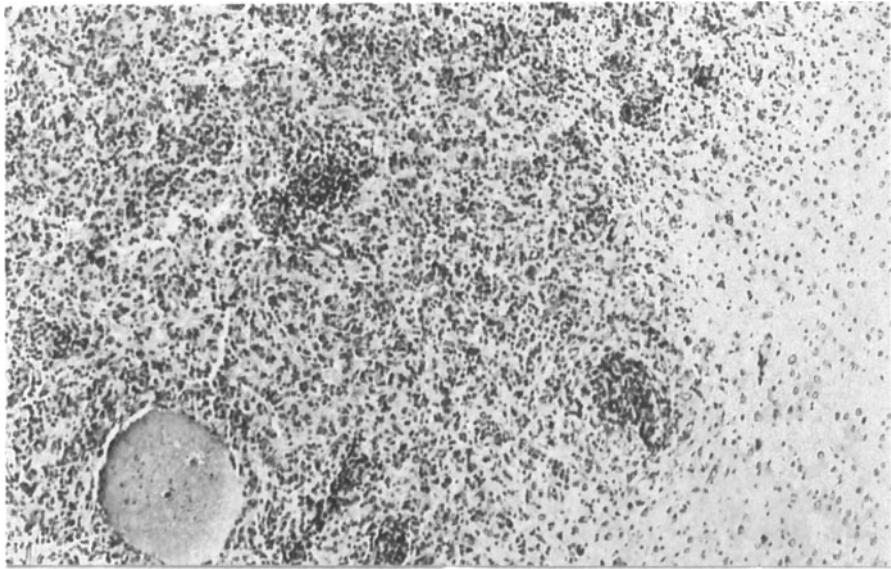
Proliferative centers with high cell density can be recognized in many microtumors and tumors (Fig. 3.5).

Neurinomas represent 41% of all experimental tumors and occur more frequently (53%) in postnatal induction experiments [3804]. They arise from Gasser's ganglion (Fig. 3.6) and from posterior spinal roots, and resemble the human ones but are more malignant and tend to diffuse in the subarachnoid spaces (Fig. 3.7). In culture, they grow rapidly, and their cells are similar to Schwann cells [593, 930, 2239]. If transplanted into subcutaneous tissue or the brain, they do not differ from those of the original tumor [594].

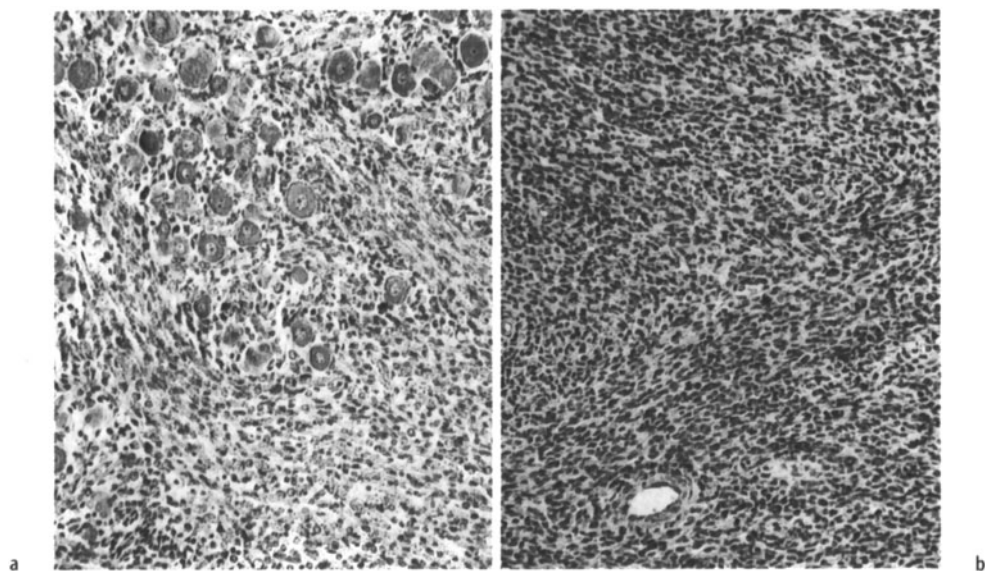
With the intraperitoneal administration of 100 mg ENU/kg in Syrian golden hamsters on the 16th day of gestation, multiple peripheral tumors, mostly subcutaneous neurofibromas, appear. They have a plexiform structure similar to neurofibromas in von Recklinghausen's disease. Simultaneously, but with lesser frequency, melanomas, pheochromocytomas, and nephroblastomas have been observed. This led to the suspicion that the target of ENU in this animal is the ganglial crests [2389]. It must be stressed that foci of melanotic cells were present in the neurofibromas. Similar tumors had already been obtained in the same animal with the combined administration of ENU through the placenta and on the skin [2597].



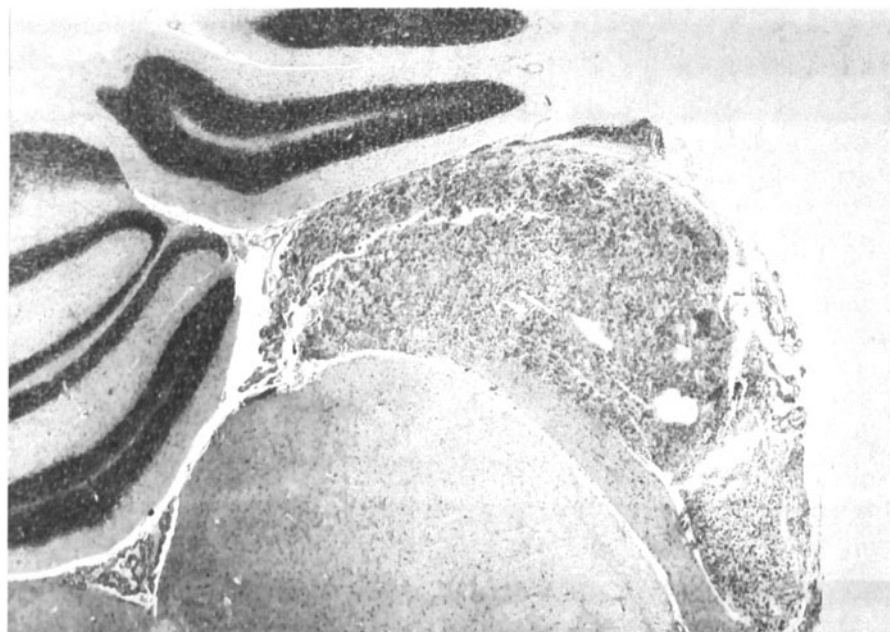
**Fig. 3.4.** General scheme of tumor development after transplacental administration of ethylnitrosourea (ENU). (From [3012])



**Fig. 3.5.** Rat transplacentally treated with ethylnitrosourea (ENU), tumor with proliferative centers. H&E,  $\times 150$



**Fig. 3.6a,b.** Rat transplacentally treated with ethylnitrosourea (ENU), neurinoma of the Gasser ganglion. **a** Ganglion cells can be recognized. H&E,  $\times 200$ . **b** Bundles of tumor cells. H&E,  $\times 200$



**Fig. 3.7.** Rat transplacentally treated with ethylnitrosourea (ENU), neurinoma of the fifth cranial nerve diffusing in the subarachnoidal space. H&E,  $\times 50$



### 3.1.2.1

#### *Pathogenesis of Nitrosourea-Induced Tumors*

The crucial moment in this model is represented by the histological latency period. However, the identification *in vivo* of the phenotypic changes of the presumed tumor cells is very difficult [1837]. This is due both to the polymorphous cellular composition of the CNS and to the fact that only a minimal fraction of the constituent cells undergoes changes leading to malignant phenotypes because of the effect of the carcinogen. It has furthermore to be taken into account that between the 17th day of *i.u.* life, when ENU is administered, and the 60th day of *e.u.* life, when the first tumors appear, the CNS undergoes substantial modifications due to the proliferation, migration, and differentiation of neuroepithelial cells which, starting from the matrix, will form the cortex and the white matter. The target of ENU is represented by the germinal zone which derives directly from the germinal layer of the neural tube [1504, 1868]. For this reason, three points have to be considered: proliferation and cellular differentiation, structural modifications of the DNA, and phenotypic alterations which occur in the target cell population.

The first point has already been considered in Chap. 1. As for the structural changes in the DNA, it is known that the most important effect of ENU is the oxygen alkylation with coupling errors during transcription, due to the substitution at the O<sup>6</sup> of guanine, O<sup>2</sup> of the cytosine, and O<sup>2</sup> and O<sup>4</sup> of the thymidine. The alkylation at the N<sup>7</sup> position of guanine and the N<sup>3</sup> of adenine may instead be responsible for the cytotoxic effects of the carcinogen [1698]. The defective ability to repair DNA seems to be responsible for the susceptibility of the CNS to the neuro-oncogenic effect of alkylating agents. Within 1 week from the administration of ENU to 10-day-old rats, the quantity of O<sup>6</sup> alkyl guanine in cerebral DNA is 20 times higher than in hepatic DNA [1139]. The effect of ENU diminishes as *e.u.* life progresses, due to the decrease in the mass of the target cells [2716]. The inefficacy of ENU administered before the 15th day of *i.u.* life is due to the fact that at this moment neuroblasts are no longer dividing, and gliogenesis has not yet started [1698].

The phenotypic changes must be discussed while taking into account that the target cells of ENU are cells of the germinal matrix, cells of the subependymal layer, the migrating glial cells, and immature subpial glial cells in the spinal cord [2384]. Short- and long-term effects can be observed in these cells. The former include cell death, nuclear pycnosis, and momentary arrest of cell division in the ventricular zone [313]. An increase of cell proliferation has to occur [1839] for a genetic fixation of the promutagenic structural changes. In fact, the cytotoxic effect of ENU is followed by cellular proliferation in the subependymal zone, in the peripheral neural plexuses and in the proximal part of the cranial nerves, especially the fifth [3356]. The roots of the fifth cranial nerve are composed of a peripheral part, with myelin of peripheral type and Schwann cells, and a central part with myelin of central type and oligodendrocytes with the line of demarcation being the zone of Obersteiner-Redig. The first proliferations of Schwann cells are observed 1 month from the administration of ENU [3625]. When tumors develop, they may simultaneously be neurinomas in the peripheral part and oligodendrogliomas in the central part of the roots, and they may often be interpenetrating [2989].

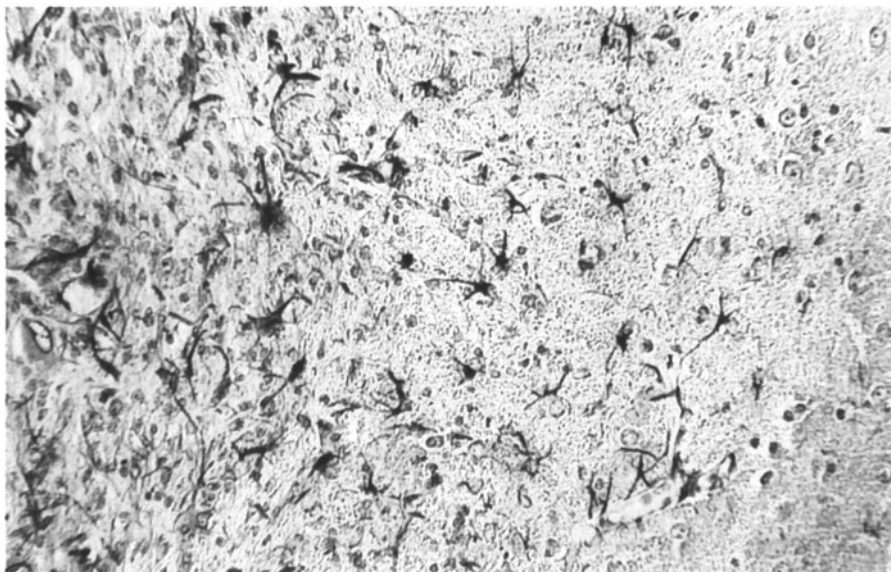
Different observations have demonstrated a cell-lineage specific mutation of the *neu/erbB2* gene in the neoplastic transformation of Schwann cells induced by transplacental ENU administration [2608, 3338, 2430]. ENU-induced trigeminal neurinomas carry a TA → AT transversion mutation at nucleotide 2012 of the transmembrane region of the *neu* gene. This mutation produces the substitution of glutamic acid for valine at codon 664 of gp185<sup>neu</sup> [149], a phosphoglycoprotein with tyrosine kinase activity and structural homology to epidermal growth factor receptor (EGFR). The mutation can be identified in trigeminal Schwann cells as early as 7 days after carcinogen administration [2430], but is always absent in the ENU-induced CNS tumors other than neurinomas [2608, 3338, 2430]. The presence of a mutated *neu* allele represents a selective advantage for Schwann cells whose proliferation rate largely exceeds that of wild-type trigeminal cells [2430]. Moreover, loss of heterozygosity for the mutant *neu/erbB2* gene, i.e., loss of the normal *neu* allele in cells previously heterozygous for the *neu* mutation, seems to represent a critical second step in the progression of ENU-induced schwannomas towards a malignant phenotype [2430].

Between the 17th day of i.u. life and the 60th day of e.u. life, no morphological change can be observed in the areas which have in the meantime developed from the ventricular zone. However, if cerebral fetal cells are put in culture after exposure to ENU in vivo, they demonstrate phenotypic modifications up to the development of tumors if they are transplanted into 5- to 10-day-old rats [1837]. If brain cells obtained when the neoplastic transformation in vivo has reached the stage of microtumors are cultured, it is still possible to find transformation in vitro [2832]. The transformation of the brain fetal cells in culture occurs in four stages, which require 100 days [1839]. Obviously, this interval is influenced by the dose of ENU administered. The cell phenotype changes before the cells become biologically malignant, i.e., before they become tumorigenic if transplanted into rats. It has to be noted that glial fibrillary acidic protein (GFAP) is negative or weakly positive in these cells [1838]. If, however, "glial maturation factor" is added to the culture, fetal glioblasts rapidly become mature astrocytes [1961, 1264].

Fetal rat brain cells exposed in vivo to ENU and transplanted into syngenic hosts after 200 days of culture form tumors which are morphologically similar to those induced with transplacental ENU [1838, 525]. Aggregates of malignant cells put into contact with the hearts of 9-day old chick embryos invade the explant. This demonstrates that invasiveness is a property associated with tumorigenicity in vivo [681, 1839].

In the period of histological latency, no morphological change is found; however, if the cells of the white matter between the ventricular germinal zone and cortex are counted on the 30th day of e.u. life, their number will be higher than in controls. Cell hyperplasias are thus recognized and represent the most precocious neoplastic manifestations [3012]. The number of mitoses is not different from controls in these areas, and the DNA histogram, obtained cytofluorometrically, demonstrates that the majority of cells are diploid. This means that cells in cycle are few, as in controls, and justifies the 30-day latency period. The labeling index (LI) with [<sup>3</sup>H]thymidine does not vary between treated and untreated animals in the subependymal cells and also remains low in the early tumor manifestations [1450, 1451].

More cell generations must take place between the moment of ENU administration and that of tumor appearance. As a matter of fact, a glial reaction elicited by trauma at the end of the latency period can enhance glioma formation [2306] and anticipate



**Fig. 3.8.** Rat transplacentally treated with ethylnitrosourea (ENU); glial fibrillary acidic protein (GFAP)-positive + reactive astrocytes confined to the periphery of an oligodendroglioma. PAP-DAB,  $\times 300$

the tumor's appearance [3034], adding some more generations of genotypically transformed cells. In the long run, however, the number and cell composition of tumors are not modified by trauma [2240, 3034].

If suspensions of fetal forebrains of rats born from i.v. ENU-treated mothers are injected into adult rat brains treated with supplementary ENU, only oligodendrogliomas develop. This may indicate that neoplastic transformation does not require pluripotent stem cells, but that it can occur on oligodendrocytes or on precursor cells committed to oligodendrocytic differentiation [399].

In experiments with MNU administered in adult rats, where tumors develop from the transformation of already differentiating and migrating glia, there is no sensitivity to the drug of the reacting glia after a stab wound; the trauma then has no influence on tumor appearance [3743].

### 3.1.2.2

#### *Cellular Composition*

ENU-induced tumors are essentially glial microtumors, ependymomas, astrocytomas, and oligodendrogliomas, both isomorphous and polymorphous.

A large number of GFAP-positive reactive astrocytes characterizes the early neoplastic manifestations [2175, 3168] (Fig. 3.1b). In microtumors and in developed tumors, practically the only GFAP-positive cells are the reactive astrocytes which, as the tumors grow, become progressively confined to the periphery and to the surrounding healthy tissue [2175, 2753] (Fig. 3.8). The scarcity of GFAP-positive tumor

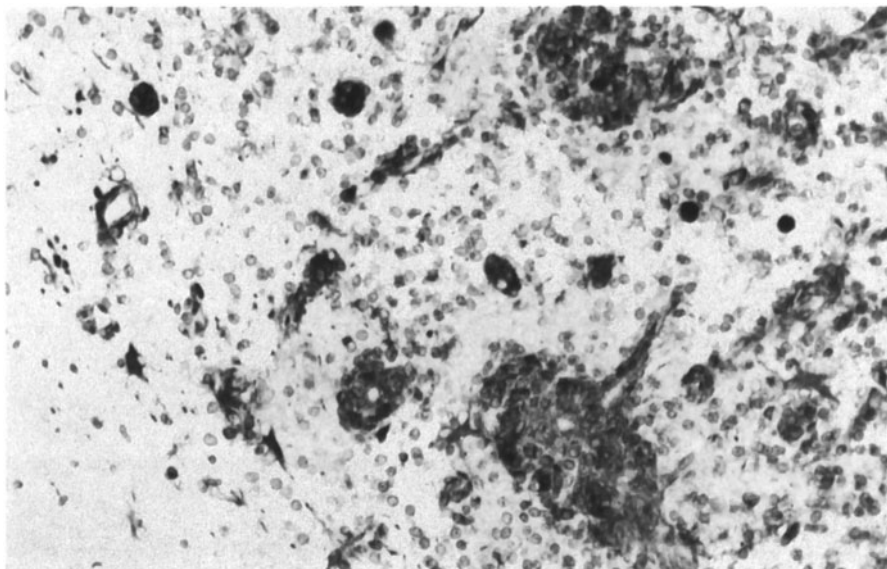


Fig. 3.9. Rat transplacentally treated with ethylnitrosourea (ENU), proliferative centers of a microtumor containing vimentin-positive cells. PAP-DAB,  $\times 300$

cells could be due both to the immaturity of the cells, which are still not capable of expressing GFAP, and to the anaplasia, meaning that the cells have lost the capacity to express GFAP [668]. The abundance of reactive astrocytes in early lesions has been variously interpreted. It could be due to the existence of hidden myelin damage [1869] or to the normal rich complement of stellate astrocytes around the ventricles. Necrotic lesions experimentally produced by trauma are equally rich in GFAP-positive reactive astrocytes [3023]. Oligodendrogliomas are the most frequent fully developed tumors and are very similar to the human ones.

Vimentin is coexpressed with GFAP in adult and reactive astrocytes [635]. However, since it appears before GFAP during cytotogenesis, it has been considered as a marker of immaturity if it is the only intermediate filament antigen expressed [3066, 241, 870]. The cells of proliferative centers of microtumors and developed tumors are vimentin-positive (Fig. 3.9) and GFAP-negative [1080, 2753]. They have been interpreted as undifferentiated elements. It is also possible that they correspond to radial glia which is vimentin-positive and GFAP-negative in the rat and a possible target of ENU, as they are already present when the drug is transplacentally administered [1081].

A precise recognition of the various cytotypes on an immunohistochemical basis is not easy. For example, carbonic anhydrase C, a typical marker for oligodendroglia [1814], (also in man [1815]), is positive in normal rat oligodendrocytes but not in tumor oligodendrocytes [1080] (Fig. 3.10). It may be that these cells are too immature to express the marker, which first appears during ontogenesis after 3 weeks of e.u. life.

With progressing growth, the tumors spread to the entire hemisphere, to the contralateral one, to the brainstem, and to the subarachnoid spaces, achieving the pic-

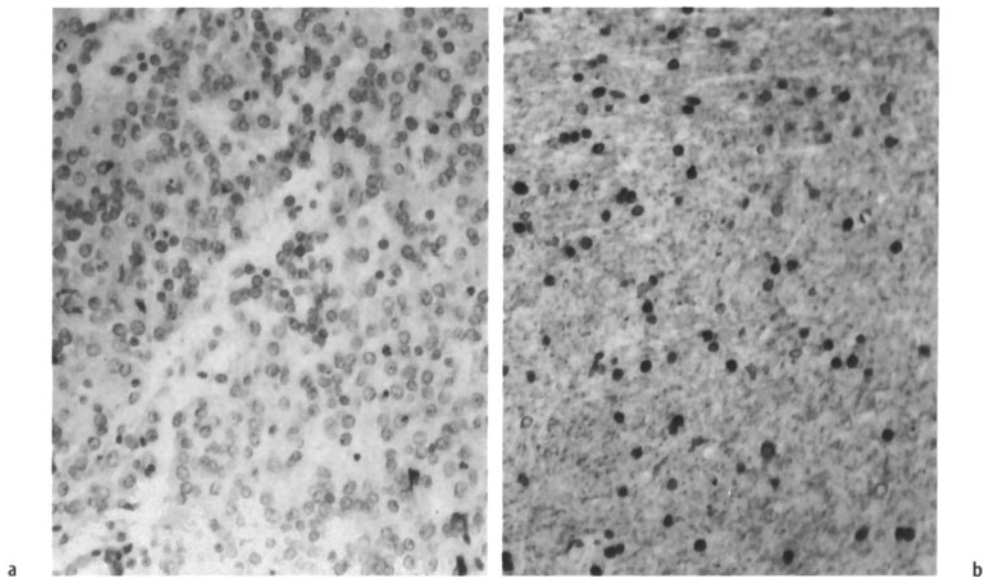


Fig. 3.10a,b. Carbonic anhydrase C. a The cells are negative in oligodendroglioma. b The cells stain positively in the normal white matter. PAP-DAB,  $\times 400$

ture of “total cancerization” of the brain. This may also be accomplished by the confluence of multiple tumors, which are often found after higher doses of carcinogen and in different stages of development. In more advanced stages, sarcomatous components develop [1502]. The tumors are therefore highly invasive. In fact, by cocultivating cells from ENU-induced tumors with fragments of normal rat brain, they progressively invade it and replace it [3305], perhaps by secreting toxic substances [3304].

Experiments with implants of cell lines of tumors, induced by ENU given transplacentally, in the brains of rats have demonstrated that there is a degradation of collagen I and III at the border zone between tumor and healthy tissue and that there is collagen of unknown origin in the extracellular matrix [2889].

In early tumor proliferations, in oligodendroglial foci, and in isomorphous oligodendrogliomas, but not in polymorphous ones, an accumulation of glycosaminoglycans (GAG) has been found with alcian blue staining techniques [2995]. The hypothesis was that oligodendroglial cells underwent neoplastic transformation after having acquired during cytogenesis the capacity to interfere with the metabolism of the GAG during myelinogenesis. In the rat, in fact, the myelination period and that of sensitivity to ENU overlap both in the brain [3012] and in the spinal cord [2384]. The involvement of oligodendroglia in neoplastic transformation had also been confirmed in the *in vivo-in vitro* system [330]. In the process of dedifferentiation this capacity may be lost.

This interpretation, however, is inconsistent with the observation that in man al-cianophilia is found in all gliomas, hence also in astrocytomas [280]. It has been explained by the presence of normal nervous tissue included in the tumor and to de-

generated areas of the tumor itself [1077]. The same interpretations can be given to alcianophilia of ENU-induced tumors [2176], and the observations have been confirmed by histoautoradiographic studies with  $\text{Na}_2\text{SO}_4$  and  $[^3\text{H}]\text{glycosamine}$  [2163]. In MNU-induced tumors, an accumulation of GAG in the tissue has been described as preceding their histological identification [831], while in ENU-induced tumors, this does not occur. It may also be that part of chondroitin sulfate, at least, is involved in cell proliferation [220]. Also, in experimental tumors, GAG may be involved in the relationship between cell motility and invasiveness and the intercellular matrix. They might be important in differentiating oncotypes.

### 3.1.2.3

#### *Vascularization of ENU-Induced Tumors*

ENU-induced tumors transplanted into rats may grow up to 3–4 mm using host blood vessels; thereafter, they must form their own vessels. In the transplant, three zones are formed: an internal avascular one, an intermediate vascular one, and a peripheral one [685, 2436]. Buds and immature capillaries are formed in the peripheral zone by “sprouting” and are not dissimilar from those found during embryonal angiogenesis [1266, 48]. All these processes may be stimulated by angiogenic factors. During normal embryonal angiogenesis, the factor believed to be active only in the earlier phases in tumor angiogenesis may also be active subsequently, hampering the differentiation of blood vessels. It has also been observed [686] that small blood vessels increase in the peripheral zone of the transplant, while endothelial hyperplasia is typical of the intermediate zone. In transplants of ENU-induced tumors in the rat, it has recently been demonstrated that there is no real increase in the number of blood vessels in the peritumoral tissue; on the contrary, there appears to be an increase in the diameter of the blood vessels towards the center of the tumor [2052]. These data are in agreement with observations on human tumors, which show that in the tissue immediately surrounding the tumor (brain adjacent to tumor, BAT) and in the infiltrated cortex, the neoformation of small blood vessels does not precede – but follows – the infiltration itself [1928, 3030].

In tumors obtained with transplanted rat glioma clones, a blood vessel density below that of normal tissue was found with an increase in the diameter of blood vessels [3117]. It must, however, be noted that in these experiments, because of their short duration, the three zones mentioned above have not been found. Similar experiments have demonstrated that the blood flow is low in both the central and peripheral zones and high in the intermediate one [3742].

### 3.1.2.4

#### *Utilization of MNU-ENU Models*

Models of autochthonous MNU tumors have been created [3053, 766]. The C6 clone obtained from a MNU induced glioblastoma [192] has been transplanted into the brain of rats in different therapeutic experiments [1623, 1467, 3757, 865], and the optimal conditions have been codified [2940].

ENU-induced tumors show a notable resemblance to human ones, but there are also many differences on the morphological level, in the prevalence of oncotypes, location, multiplicity or uniformity [1867]. Fundamental is the consideration that ENU-induced tumors are produced by administering the carcinogen at a precise moment of cytogenesis, while human ones may derive through a constant exposure of target cells to possible carcinogens. Nevertheless, the pathogenetic mechanisms recognizable in the experimental model may be hypothesized for human tumors of the adult, but much less so for the infantile ones. The concept of genotypically transformed “stem cells” may explain the onset of tumors at any time.

The ENU model has been useful in neurooncology more for studies on the genesis of tumors than for therapeutic applications for which more simple and reliable models, such as the MNU or avian sarcoma virus (ASV) astrocytoma, are preferable [3081]. The occurrence of multiple tumors and the impossibility of knowing all tumor parameters *in vivo* are the most important failings. However, radiotherapy experiments utilizing explants of ENU-induced tumors have been carried out [1043, 3270]. Irradiation after neonatal administration of ENU has caused a decrease in the incidence of the tumors [1722]. Carmustine (BCNU), lomustine (CCNU), and other chemotherapeutic derivatives of nitrosourea administered to rats born of ENU-treated mothers cause a decrease and a delay in the development of the tumors [3009]. If nerve growth factor (NGF) is administered before or after ENU, a lower number of neurinomas at the 90th day of *e.u.* life is obtained [3550].

## 3.2

### Viral Carcinogenesis

Up to now, no virus has been etiologically associated with cerebral tumors in the traditional sense. Instead, it is possible to produce tumors experimentally with a certain variety of virus. Among DNA viruses, adenoviruses and papovaviruses are those most efficaciously used. Human adenovirus-12 causes tumors in various animals after intracerebral or intraorbital inoculation and after different latency periods. The tumors produced are malignant and undifferentiated, of sarcomatous type or neuroblastomas and retinoblastomas [2344, 2345].

With the same virus, PNS embryonal neuroepithelial tumors have been obtained in rodents after intraperitoneal inoculation [2476]. The tumors demonstrated multiple morphological differentiations. Simian adenovirus (SA7), which produces tumors difficult to classify [3220], simian virus 20 (SV20), chicken-embryo-lethal orphan (CELO) viruses, etc., have also been inoculated intracerebrally.

Papovaviruses isolated from human cases of progressive multifocal leukoencephalopathy produce tumors, among which are mainly cerebellar medulloblastomas [2534]. JC, EK, BK, and MNV strains of papovavirus, which produce ependymomas, have also been employed [571, 381]. Nonhuman papovaviruses such as the bovine papillomavirus (BPV) have also been demonstrated to be useful. Polyomavirus and simian vacuolating virus (SV40) have been tried as well (Fig. 3.11). In particular, in hamsters, medulloblastomas were induced by JCV which is a human DNA virus of polyoma type.

Among the RNA viruses (oncoviruses, retroviruses) the avian sarcomavirus (ASV), the murine sarcomavirus, and the simian sarcomavirus have to be consid-

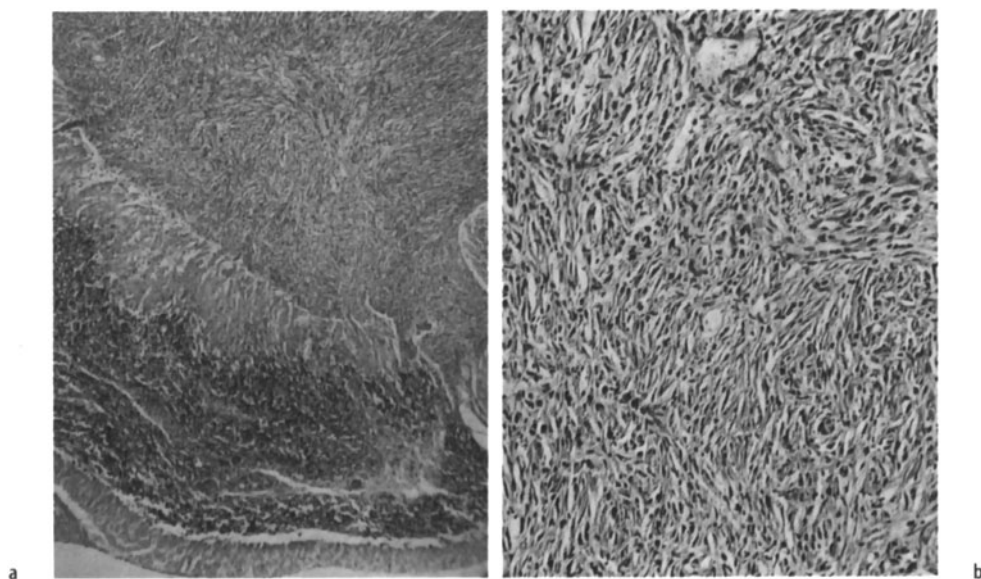


Fig. 3.11a,b. Tumor induction by simian virus SV40 in hamster. a Location in the posterior fossa. H&E,  $\times 50$ . b Meniomatous aspect. H&E,  $\times 200$ . (From [2994])

ered. The most frequently utilized has been the ASV [568]. Since the first gliomas obtained by Rabotti and Raine [2350], the production of experimental tumors, especially with C and D subgroups, has been codified in different animals. Sarcomas have been obtained in the chicken, astrocytomas and sarcomas in mammals; in the dog and rat, most of the tumors have been anaplastic astrocytomas if the inoculation was into the cortex or the subependymal zone. The ASV model represents one of the best in that it fulfils a whole series of criteria: it is glial, spontaneous, and intraparenchymal, and it may be cultivated in vitro and transplanted subcutaneously or into the brain. It has allowed a whole series of immunological and chemotherapeutic experiments [243, 381].

Because of the biological similarities between monkey and man and the better possibility of manipulation in the former, an experimental model has always been advocated in this animal. Positive results have been obtained with the Rous sarcoma-virus [1503, 1805, 2789]. The model seems to have been perfected in *Macaca fuscata* [3364].

### 3.3 Transplantable Animal Models

Various modalities have been followed. First of all, there are syngeneic tumors, i.e., tumors which are independently produced with chemical or viral carcinogens and then transplanted into syngenic animals. Another modality is that of heterotransplants carried out in immunologically incompetent animals or at such privileged



sites as the brain, anterior chamber of the eye, or facial pouch in normal animals. A typical example of an immunologically incompetent animal is the athymic mouse. The great advantage of these models is given by the uniformity of experimental conditions which can be obtained.

Among the syngeneic transplantable tumors there are, first of all, those induced in the rat with polycyclic hydrocarbons, such as murine ependymoblastoma and types 26 and 261 murine glioma, and those induced in the rat with nitrosourea, C6, 9L, and RG-2. Ependymoblastoma has been the object of numerous chemotherapeutic studies [3145, 109, 1044], even though it is hardly comparable with human tumors.

Among nitrosourea-induced tumors, the most frequently used have been the C6 glioma, the MNU-induced 9L gliosarcoma, and the ENU-induced RG-2 glioma. The C6 has been found to be unstable in its cellular type [595]; however, it has been used in different experiments for various purposes [1622, 1621, 865, 3757, 1467]. The model characteristics have been improved in order to use it for therapeutic studies [2940]. The 9L has found more consensus for kinetic cellular studies, radiotherapy, and chemotherapy [2839]. The RG-2 has a stable cellular population [3628].

Other syngenic models include the spontaneous murine VM astrocytoma which occurs in inbred VM-dk mice [949] and the anaplastic astrocytoma induced by the Schmidt-Ruppin ASV. The spontaneous VM mouse astrocytoma corresponds to the criteria of the ideal model of Wilson [3690], because it is glial and spontaneous. It was seldom used as it was limited to in vivo experimentation. Cell lines have, however, been established [3127] and characterized [2644, 2645]. The cells which most resemble normal astrocytes are the less tumorigenic ones if injected intracerebrally in syngenic animals, while the opposite holds true for the less differentiated ones. This line, VMDKP 497, is heterogeneous and has produced six clones different from each other [647], with characteristics varying from astrocytic to anaplastic. Five of these have been found to be tumorigenic when injected into syngenic animals [1750].

The heterotransplants have received a great impulse because of the advent of the "nude mouse" model, into which both tumors and permanent cultured cell lines may be directly transplanted; the morphology, karyotype, and antigenic model are maintained. Glioblastomas, astrocytomas, gliosarcomas, meningiomas, etc., have thus been grown. In general, the constancy of the morphological similarity with original human tumors has been emphasized [2727, 3610], even if different opinions are not lacking [2751]. Chemotherapy [3081] and radiotherapy [3147] evaluation studies have been carried out with these models. Cell lines derived from gliomas grow without changing their morphology.

### 3.4

#### Gene Transfer Models of Neural Tumors

Experimental models obtained by genetic manipulation appear to be highly promising for identifying in vivo effects of isolated genes and for studying molecular pathogenetic mechanisms. Transgenic mice are obtained by microinjection of genetically manipulated embryonal stem cells into fertilized murine ova [1493]. As a consequence of the stable integration of DNA in the zygote, all somatic and germ cells of these animals contain single or multiple copies of the transgene. A different method

of gene transfer, which gives rise to chimeric animals, employs introduction of DNA constructs into embryonal stem cells and transfer of these cells into blastocyst stage embryos [2962A]. Recently, a third experimental model has been developed which utilizes a retrovirus-mediated gene transfer into neural transplants [1701, 22]. Using a replication-defective retroviral vector, foreign transforming genes are introduced into fetal rat brain cells which are grafted intracerebrally into syngenic host animals. These transplants develop with formation of pseudocortical highly differentiated architectures and provide a good model to study the expression of retrovirally transmitted genes in different CNS cell types. Several oncogenes have been introduced by this route into fetal brain transplants (polyoma *medium T* gene, *v-src*, human *K-fgf/hst*, SV40 *large-T* gene, *v-Ha-ras*, *v-myc*), demonstrating a cell-type specific transformation potential [3671]. Hemangiomas and anaplastic gliomas have been obtained with polyoma *medium-T* gene, different glial tumors and sarcomas with *v-src*, and capillary angiomas with *K-fgf/hst*, a protooncogene encoding a member of the fibroblast growth factor family. Transfer of SV40 *large-T* gene into CNS grafts produced primitive neuroectodermal tumors (PNET) similar to human medulloblastomas [22]. In agreement with this finding, different recent experiments using transgenic mice indicate that the expression of SV40 *large-T* antigen can induce brain tumors such as PNET of the pineal gland, retinoblastomas, and choroid plexus papillomas [3418, 999].

The simultaneous introduction of *v-Ha-ras* and *v-myc* into fetal brain transplants have demonstrated a significant complementary transforming effect of these two oncogenes [22]. In fact, the simultaneous expression of both oncogenes in fetal brain transplants induced, after a short latency period, multiple highly anaplastic undifferentiated tumors, composed of cells with a limited potential for astrocytic differentiation. On the contrary, transfer of retroviral vectors harboring only *v-gag/myc* sequences produced rare tumors with features of PNET, whereas *v-Ha-ras* alone induced anaplastic astrocytomas after a long latency period [3671]. A complementary transforming effect of *ras* and *myc* has been observed also in later stages of CNS development [3671]. Microinjection of the retroviral vector harboring both oncogenes into the brain of newborn rats induced different tumors, including PNET, hemangioendotheliomas, and gliomas. The occurrence of PNET in this experiment is of particular interest because it suggests that neural progenitor cells, which are the target of the neoplastic transformation, persist in the newborn rat brain [3671].

## Antigens of Phenotypic Expression and Differentiation Markers

The diagnosis of brain tumors is based on the recognition of phenotypes which are typical of a cytogenetic line in a given differentiation stage. This recognition is not easy, because the nervous system is composed of a variety of cell types which may derive from common precursor cells. Neoplastic transformation modifies cell phenotypes, usually towards less mature stages. It would be very useful to have markers which characterize every cytotype in the different maturation stages or even only specific markers of some oncotypes.

The study of structural and surface antigens has produced a tremendous amount of data in this field. The technology of monoclonal antibodies (mAb) has provided a large quantity of antibodies towards specific antigenic determinants. Of particular value has been the identification of various antigens of nervous cytotypes during cytogenesis [2704, 806, 1842, 948, 1267, 1634, 2968, 3067, 1333], even though they have been studied mostly in normal cells in culture and only rarely in tumors.

### 4.1 Brain Tumor-Associated Antigens

In the late 1960s, glioma-specific rabbit sera began to be produced [2068, 2067, 536], but the results were poor, because they contained a heterogeneous mixture of antibodies without a tumor specific binding. The technique of mAb represented a great improvement in this regard and today the number of mAb against tumor-associated antigens is countless. It goes beyond the goal of this book to list them. It must be said that their specificity is evaluable only in relation to the patterns of staining described in the different tissues and under particular physiological and pathological conditions. It may also happen that mAb produced in different laboratories, and differently labeled, recognize the same antigens. Complete reviews of these problems are available [683, 382, 537, 3676, 682].

Most antibodies against tumor-associated antigens recognize the following categories of antigen: (a) biochemically defined antigens, including structural proteins, such as intermediate filaments, or enzymes, like neuron specific enolase; (b) antigens common to different tumors and tissues of neuroectodermal origin, both central and peripheral [1951, 414, 3755, 683]; (c) glial antigens, expressed mainly by glioma cells, but also by reactive astrocytes and other nonneuroectodermal tissues [682]; (d) oncofetal antigens, typical of fetal tissues and expressed in the adult only in tumor cells [3675]; (e) lymphoid differentiation antigens, expressed by circulating lymphocytes and by cells of malignant gliomas [1160, 1632, 682], such as HNK-1 antigen.

The possibility of utilizing them *in vivo* for diagnostic purposes is limited. Tumors and especially gliomas are heterogeneous and antigenically complex [3138, 242, 3674, 3676], so that the probability for an antigen to be expressed in the same way by all gliomas of a given type is not high; moreover, the quantity of cells expressing a single antigen in a glioma cannot be determined.

mAb are often produced from cultured tumor cells which represent only partially the antigenicity of the tumors *in vivo*. The growth *in vitro*, moreover, can modify the cell surface, either introducing new antigens or eliminating antigens, so that the antigenic heterogeneity may be increased [3676]. Most antigens are expressed also by normal cells in various tissues, and all the possible specificities of mAb against tumor-associated antigens can be demonstrated only by *in vivo* studies, while not considering the fact that surface antigens usually do not tolerate routine fixation and embedding procedures.

The pattern of expression in human astrocytomas of two typical cell-surface antigens (A4 and A010) has been recently described [1027]. It has been shown that they are expressed in a large proportion of astrocytomas as well as in some normal cells of different origin.

## 4.2

### Antigens Employed in the Histological Diagnosis of Brain Tumors

This chapter deals with those markers which are used routinely for tumor diagnosis and not with all the markers offered today by immunohistochemistry. Every kind of protein can be demonstrated by antibodies, and the scope of immunohistochemistry now includes many proteins codified by oncogenes and tumor suppressor genes involved in malignant transformation, in signal transduction, and in the control of cell proliferation [2992].

Currently, the number of markers used in the routine diagnostic procedure is roughly 30.

Complete reviews are available on this subject [298, 667, 3021, 2614, 2174]. Immunohistochemistry is today routinely applied and must be regarded as an indispensable diagnostic tool; however, some precautions must be taken. Polyclonal antisera contain a large amount of immunoglobulin (Ig) against different regions of the same antigenic molecule and also against molecules different from the antigen employed in the immunization. mAb contain one type of Ig against a single epitope, so that they are more specific, even though their specificity is not absolute.

Applying immunohistochemistry to brain tumors, it is necessary above all to demonstrate the specificity of mAb, since rat Ig may nonspecifically bind astrocytes and myelin sheaths [2522, 2612]. This can be obtained by immunoblotting; controls, moreover, must be performed by preabsorbing primary antibodies with the corresponding antigen or substituting the antibody with class-specific Ig. It must be taken into account that mAb are more specific than antisera, but generally they are also less sensitive [1317], so that in material processed for histology, since the epitope may be destroyed or lacking, an antigenic protein has a greater probability of being revealed by antisera. The best "immunohistochemical reagent" would be a mixture of mAb against different antigenic determinants of the same molecule [298].

In histological material, many antibodies are useless because of false negative reactions due to fixation. All fixatives affect the molecular structure of antigens to greater or lesser degree, destroying the antigenic sites or simply masking the antigen or making it inaccessible to antibodies [357, 2243, 2178, 2697]. Sometimes it is useful to perform a predigestion of the tissue in order to avoid the antigen masking [357, 2243, 2201, 2178]. This can be done, for example, for factor VIII/RAg, fibronectin, and laminin with collagenase [2178]. However, many antigens do not tolerate fixation, so they must be demonstrated on frozen sections. This is true especially for surface antigens. It is interesting to note that 35 different mAb against intermediate filaments systematically studied on cryostat sections of brain tumors gave unexpected reactivities. Four major sources of the artifactual staining were found, suggesting care is indeed needed in interpreting immunohistochemical results in brain and tumors [946]. Microwave irradiation is today a facilitating tool [453a].

The ultrastructural localization of cell-specific antigens by immune electron microscopy may be helpful in either confirming the antigen specificity or giving information on the cell biology.

#### 4.2.1

##### Glial Markers

#### 4.2.1.1

##### *S-100 Protein*

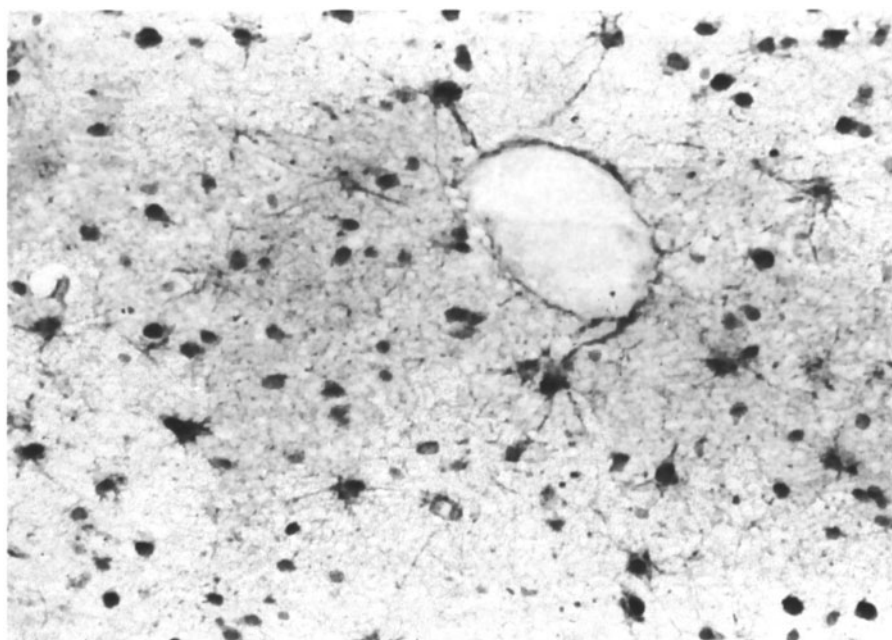
S-100 is an acid protein of low molecular weight (20–25 kDa), composed of two distinct subunits, an  $\alpha$ -subunit (S-100 $\alpha$ ) and a  $\beta$ -subunit (S-100 $\beta$ ). The name is due to its solubility in 100% ammonium sulfate [2388].

Considered at first as specific for the nervous system, it has now been found in many normal, nonnervous cells: chondrocytes, adipocytes, myoepithelial cells of the mammary gland, Langerhans cells, melanocytes, etc. There is no general agreement regarding its occurrence in neurons [3365, 1445]. It is considered more a glial than a neuronal marker, being positive in astrocytes (Fig. 4.1) [2169, 2040, 1445], oligodendrocytes [2040], and ependymal cells [2388]. In the peripheral nervous system (PNS), Schwann cells and satellite cells are positive [2387, 3294].

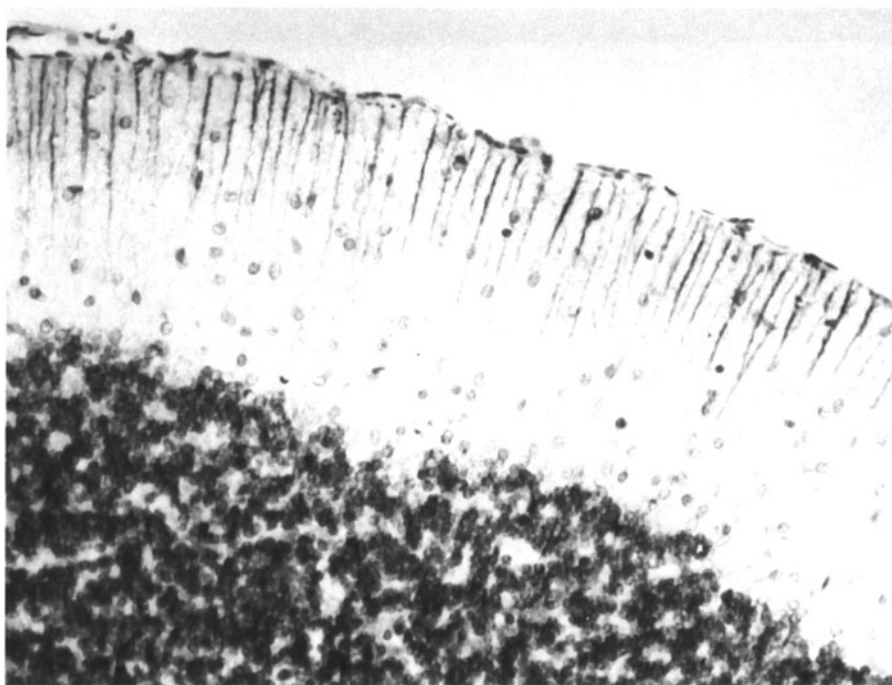
From the many studies on cerebral tumors [1215, 2391, 3640, 3375] it can be deduced that: (a) in astrocytic tumors the protein content decreases with increasing anaplasia, so that in glioblastoma there are few positive cells; in ependymomas and oligodendrogliomas only occasionally are positive cells found [825]; (b) neurinoma cells are strongly positive [3294], but the usefulness of the marker in the differential diagnosis of the malignant form is limited [3294, 3640].

The documented occurrence of the protein in many extranevous tumors, carcinomas included [2387, 2388, 3640], obliges one to use great caution in the diagnosis of brain tumors [298, 841].

The two subunits,  $\alpha$  and  $\beta$ , show a different distribution in brain tumors; the  $\beta$ -subunit decreases with malignancy, whereas the  $\alpha$ -subunit varies [1270]. This might be helpful in diagnostic procedures.



a



b

Fig. 4.1. a S-100 protein-positive reactive astrocytes. PAP-DAB,  $\times 30$ . b Glial fibrillary acidic protein (GFAP)-positive Bergmann's gliosis. PAP-DAB,  $\times 300$

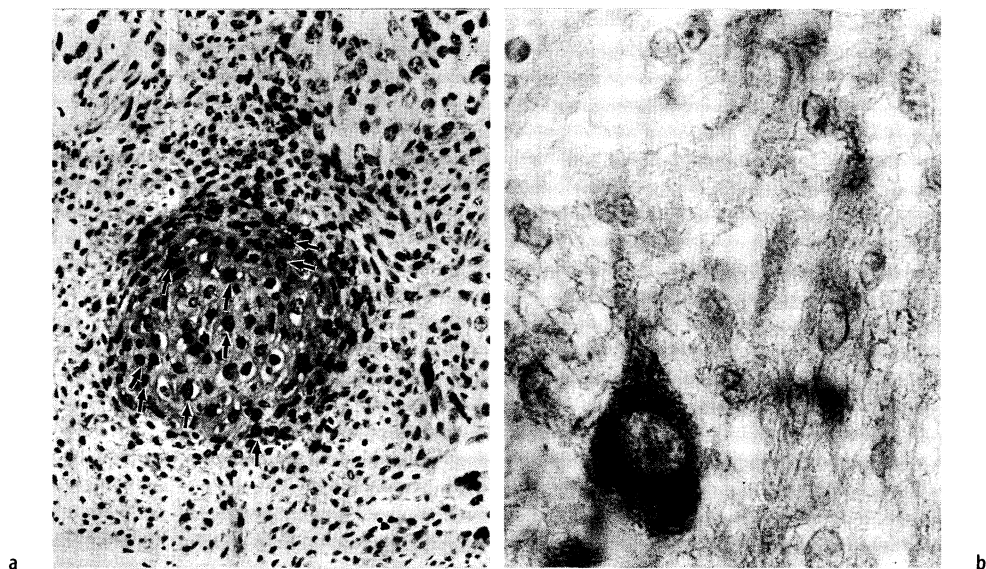


Fig. 4.2. **a** Glial fibrillary acidic protein (GFAP)-positive cartilage in a teratoma. PAP-DAB,  $\times 200$ . **b** Neuron-specific enolase (NSE)-positive reaction in neurons of a gangliocytoma. PAP-DAB,  $\times 1000$

#### 4.2.1.2

##### *Glial Fibrillary Acidic Protein*

Glial fibrillary acidic protein (GFAP) is the most studied and utilized glial marker. Its partially hydrosoluble protein was initially purified from plaques of multiple sclerosis [829] and subsequently also from normal white matter [636]. The molecular weight is about 50 kDa, and the protein represents the chemical subunit which characterizes gliofilaments. The latter are a subclass of intermediate filaments (IF) which includes a group of filamentous proteins with a diameter of approximately 10 nm. The other IF are vimentin, neurofilaments (NF), desmin, and keratin, each of which shows a peculiar cell distribution [1005, 1887, 1149]; GFAP is present only in glial cells, NF only on neurons, desmin in the muscle tissue and keratin in epithelial cells. Vimentin, mainly found in mesodermal cells, has been identified in cells of every embryologic derivation and, characteristically, in vitro cultured cells [945].

Proteins of the different IF belong to a multigenic family and share some amino acid sequences [2696, 1040], so that immunohistochemically some antisera and mAb may react with more than one IF. There may be a cross-reaction for GFAP and vimentin for every antibody produced against both antigens [2696, 2723].

In the CNS, antisera and mAb against GFAP stain specifically normal and reactive astrocytes (see Fig. 4.11a) of the gray and white matter and Bergmann's glia in man, mammals, and other vertebrates [636] (Fig. 4.2). Occasionally, unexpected staining has been observed outside the CNS, i.e., Schwann cells, enteric cells, cells of salivary

gland tumors [376], chondrocytes of normal epiglottis, and of cartilage tissue found in glial tumors [1654] and in teratomas [2174, 2460] (Fig. 4.2a).

The interpretation of these findings is not easy, once proven that they are not artifactual. However, the usefulness of GFAP as a marker of glial tumors remains beyond doubt.

GFAP in brain tumors has been widely studied [783, 2171, 692, 3507, 668, 3533, 1196, 3018]. It is positive in all astrocytic tumors (Fig. 4.3a), pleomorphic xanthoastrocytoma [1650], subependymal giant cell astrocytoma [2390, 302], astroblastomas [692, 1196, 3018] and subependymomas [3018] included, as well as in the glial component of gliosarcomas, sarcogliomas and gangliogliomas [1846, 3020]. Also, ependymomas and oligodendrogliomas contain GFAP-positive cells [692, 828, 1307, 784, 668] for reasons which will be discussed in the relevant chapters.

Nonglial tumors may also contain GFAP-positive cells, such as cerebellar hemangioblastomas [692, 691, 43], medulloblastomas [2096, 2550, 3042, 1078, 2815], and plexus-papillomas [2878, 3394]. In the first tumor, reactive astrocytes or stromal cells which phagocytosed GFAP from the microenvironment [691, 3021] may be responsible; in plexus-papilloma GFAP is sometimes coexpressed with cytokeratin [741] and is interpreted as a sign of focal ependymal differentiation. Neurinomas also may contain GFAP-positive cells [3398, 2234, 1143, 2752] in line with the positivity of some normal Schwann cells [639, 1540, 8].

With immunoelectron microscopy, GFAP can be demonstrated by the immunogold technique on IF [2260] (Fig. 4.4).

Complete reviews of the subject are available [2215, 827].

#### 4.2.1.3

##### *Glutamine Synthetase*

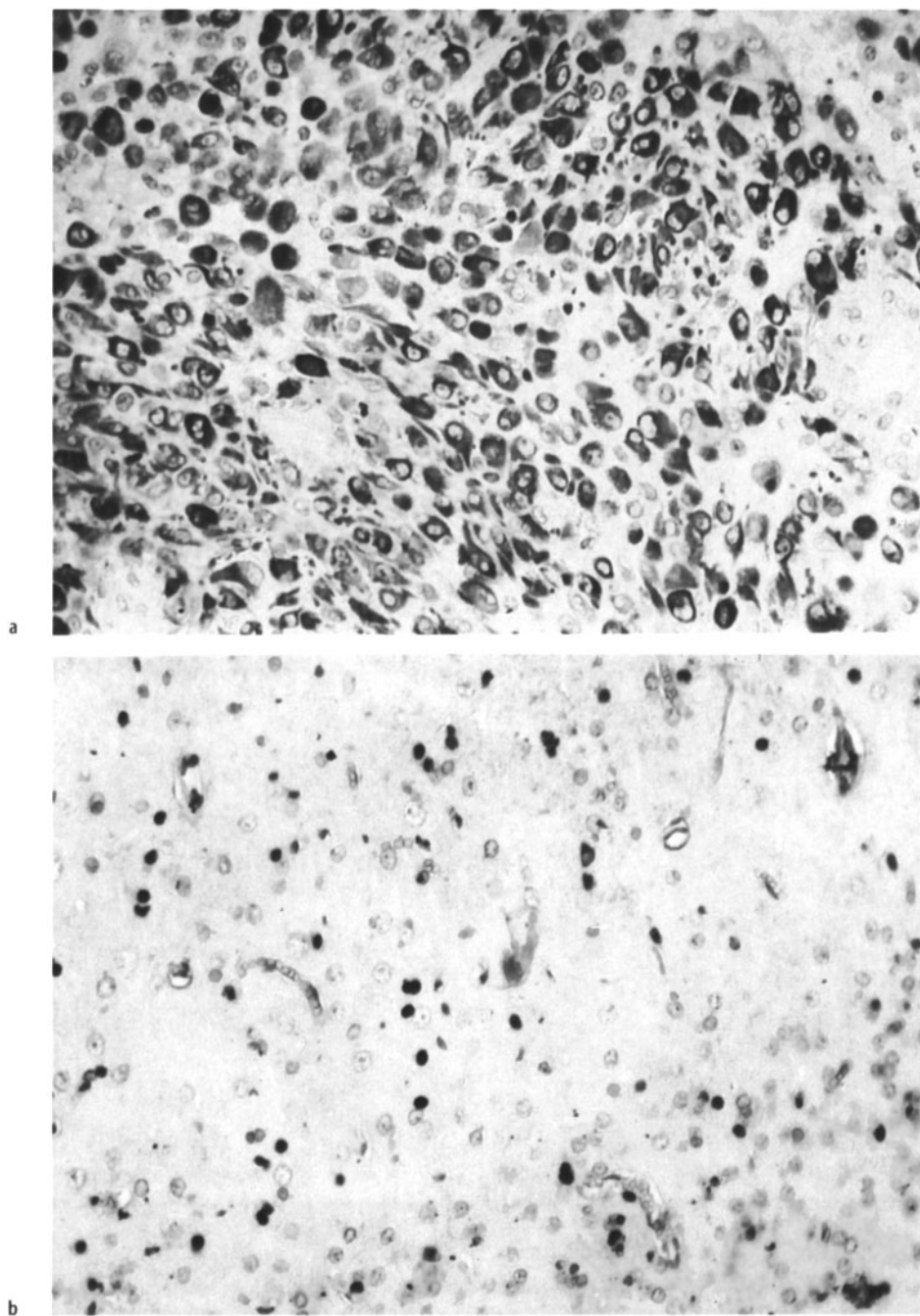
Glutamine synthetase (GS) is an enzyme which has been localized in glial [2454] and retinal cells and has been considered as a specific marker for rat CNS astrocytes [2452]. It is diffusely positive in astrocytomas, inversely proportional to anaplasia, scarcely positive in ependymomas, and negative in oligodendrogliomas and meningiomas. Groups of cells may be positive in medulloblastoma. The usefulness of GS in the diagnosis of brain tumors is limited by the observation that the enzyme is also positive in such cells of other human tissues as hepatocytes [2643].

#### 4.2.1.4

##### *Carbonic Anhydrase*

Carbonic anhydrase (CA.C) is an enzyme which is widely diffused in nature. It occurs in animal cells as two isoenzymes. In the CNS the isoenzyme C is present, localized in the human [1815] and murine [1814] oligodendroglia (Fig. 4.3b) and in Müller's cells of the retina. Human and experimental oligodendrogliomas, however, do not stain [1080].





**Fig. 4.3. a** Glial fibrillary acidic protein (GFAP)-positive reaction in tumor astrocytes and their processes in human astrocytoma. **b** Carbonic anhydrase C-positive reaction in normal oligodendrocytes of rat brain. PAP-DAB,  $\times 400$

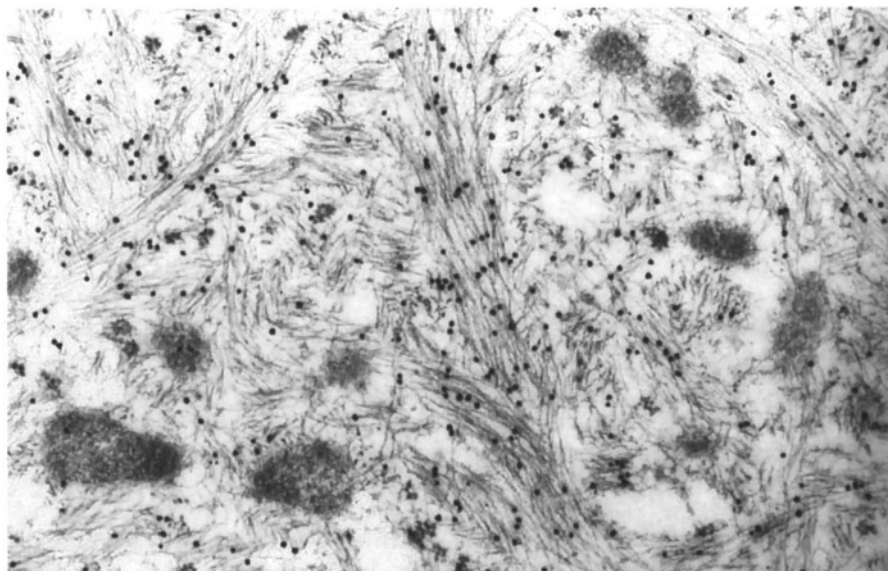


Fig. 4.4. Human astrocytoma, immunogold staining for glial fibrillary acidic protein (GFAP) on intermediate filaments (IF),  $\times 60\,000$

#### 4.2.1.5

##### *Myelin Basic Protein*

Myelin basic protein (MBP) is present in the rat myelin by the tenth day of extrauterine (e.u.) life. It has been immunohistochemically demonstrated in the cell body and processes of oligodendrocytes of the newborn rat [3308, 3309]. It is seen also in human immature oligodendrocytes, but never in the human adult oligodendroglia [1477]. There is some evidence of MBP positivity in human oligodendrogliomas [2238]. We and others have found these tumors to be MBP-negative [298, 667].

#### 4.2.1.6

##### *Myelin-Associated Glycoprotein*

Myelin-associated glycoprotein (MAG) is present in central and peripheral myelin, in Schwann cells, and in immature oligodendroglia. It is correlated with antigen HNK-1 and recognized by antibody Leu-7, which in turn also recognizes an epitope of MAG [2444]. Human oligodendrogliomas are generally MAG negative [2904].

#### 4.2.2

##### Neuronal Markers

#### 4.2.2.1

##### *Neuronal-Specific Enolase*

Enolase isoenzymes are a group of five dimeric proteins, a combination of three subunits from 40 to 50 kDa, belonging to the glycolytic pathway where they catalyze the interconversion of 2-phospho-d-glycerate and phosphoenolpyruvate [2102]. Neuronal-specific enolase (NSE) is a homodimer composed of 2  $\gamma$ -subunits, once called protein 14.3.2. Under normal conditions NSE is restricted to CNS and PNS neurons, but when applied to tumors it gave good results [298]. Cells of the APUD system also showed positivity for the markers [2102]. This has been regarded as a specific marker of neurons, axons, and neuroendocrine cells [3048, 1994]. Widely used in the diagnosis of neuroendocrine tumors, its usefulness in diagnosing brain tumors is controversial, because although it may be positive in tumors with neuronal differentiation (Fig. 4.2b) such as medulloblastomas or central neuroblastomas, it may also be positive in normal nonneuronal cells [1216], in reactive astrocytes of malignant glial tumors and in nonneuroepithelial tumors [298, 3130]. Its specificity may be strongly decreased in pathologic conditions and tumors, even though different staining patterns and specificities have been shown between mAb and polyclonal antisera [3130].

#### 4.2.2.2

##### *Neurofilaments*

Neurofilaments are the IF of neurons, composed of a triplet of proteins of different molecular weight, 68, 150, and 200 kDa. These proteins are not regularly distributed, either among the different populations of neurons or inside single neurons. The 200 kDa subunit is the main component of axons and not observed in dendrites or cell bodies of cortical or hippocampal neurons, whereas the 68 kDa subunit is typical of cell bodies and dendrites of Purkinje cells (Fig. 4.5). Very important for their localization is the phosphorylation of NF; phosphorylated and nonphosphorylated forms distribute differently in axons and cell bodies [3307]. In human tumors, NF are positive when ganglion cells or a neuronal differentiation are present, such as ganglioneuroblastomas, gangliocytomas, gangliogliomas, pheochromocytomas [2815, 2343, 2174, 3463, 3464], teratomas (Fig. 4.5b), and in tumors of neuroendocrine origin, such as carcinoid tumors, paragangliomas, and oat-cell pulmonary carcinomas.

Paraffin embedding and fixation are limiting factors in the demonstration of NF. In frozen sections they are, in fact, demonstrable in many tumors and reveal a neuronal differentiation where it was not suspected [1145], for example, in primitive neuroepithelial tumors.

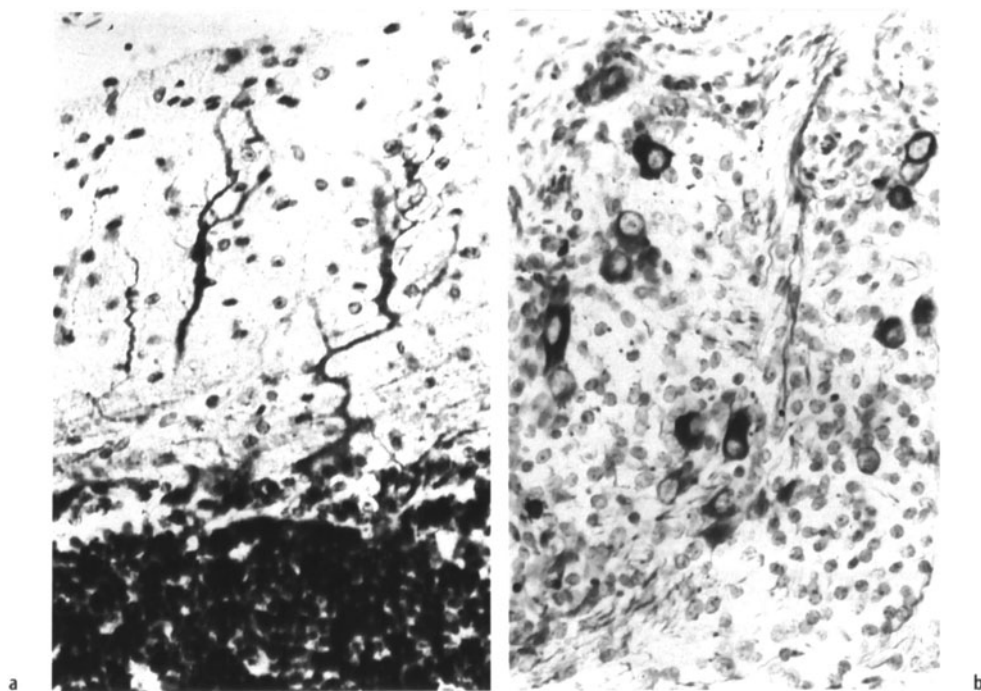


Fig. 4.5a,b. Positive reaction for neurofilaments (NF) in a apical dendrites of Purkinje cells and b neurons of a teratoma. SM31 antibody. ABC-DAB,  $\times 400$

#### 4.2.2.3

##### *Synaptophysin and Chromogranin*

Synaptophysin is a 38-kDa glycoprotein found in synaptic vesicle membranes [3669, 1495, 2269] and playing a major role in synaptic vesicle exocytosis [3458], which appears to be a reliable and specific marker for neuronal and neuroendocrine tumors, useful in fixed and paraffin-embedded tissues [2269]. It has been demonstrated in gangliogliomas, gangliocytomas, primitive neuroectodermal tumors (PNET), including medulloblastomas [3103, 1145], and neurocytomas [3563]. Its expression is prominent in ganglion cells of these tumors, due to their increase during maturation. The reliability, however, is reduced when ganglion cells are absent.

Chromogranin is the major protein isolated from vesicles in adrenal chromaffin cells [3260]. It has been demonstrated in a variety of neuroendocrine cells and tumors, and also in neurons of the CNS and PNS, but never in tumors of the CNS.

#### 4.2.3

##### **Markers Nonspecific for the Nervous System**

HNK-1 (mAb Leu-7) was at first considered a marker specific for human natural killer cells. Since it also reacts with myelin, oligodendrocytes, and Schwann cells, HNK-1

has been proposed as a marker for oligodendrogliomas [2338]. Leu-7 has actually been shown to stain human oligodendrogliomas intensely, as well as other neuroectodermal tumors [2613, 2752] and carcinomas of various origin. In spite of the diffuse cross-reactivity, it is considered useful to solve specific problems, for example, the distinction between a Leu-7-negative meningioma and a positive oligodendroglioma invading the meninges [2874].

Anti-Leu-M1 (MMA) is another hematopoietic-specific antibody which cross-reacts with anti-Leu-7 and anti-Leu-11a (NKP-15), is partially positive in astrocytomas and oligodendrogliomas, and is intensely positive in ependymomas [3363]. It recognizes cell surface epitopes of monocytes, granulocytes, and activated T lymphocytes [1235].

#### 4.2.4

##### Vessel Markers

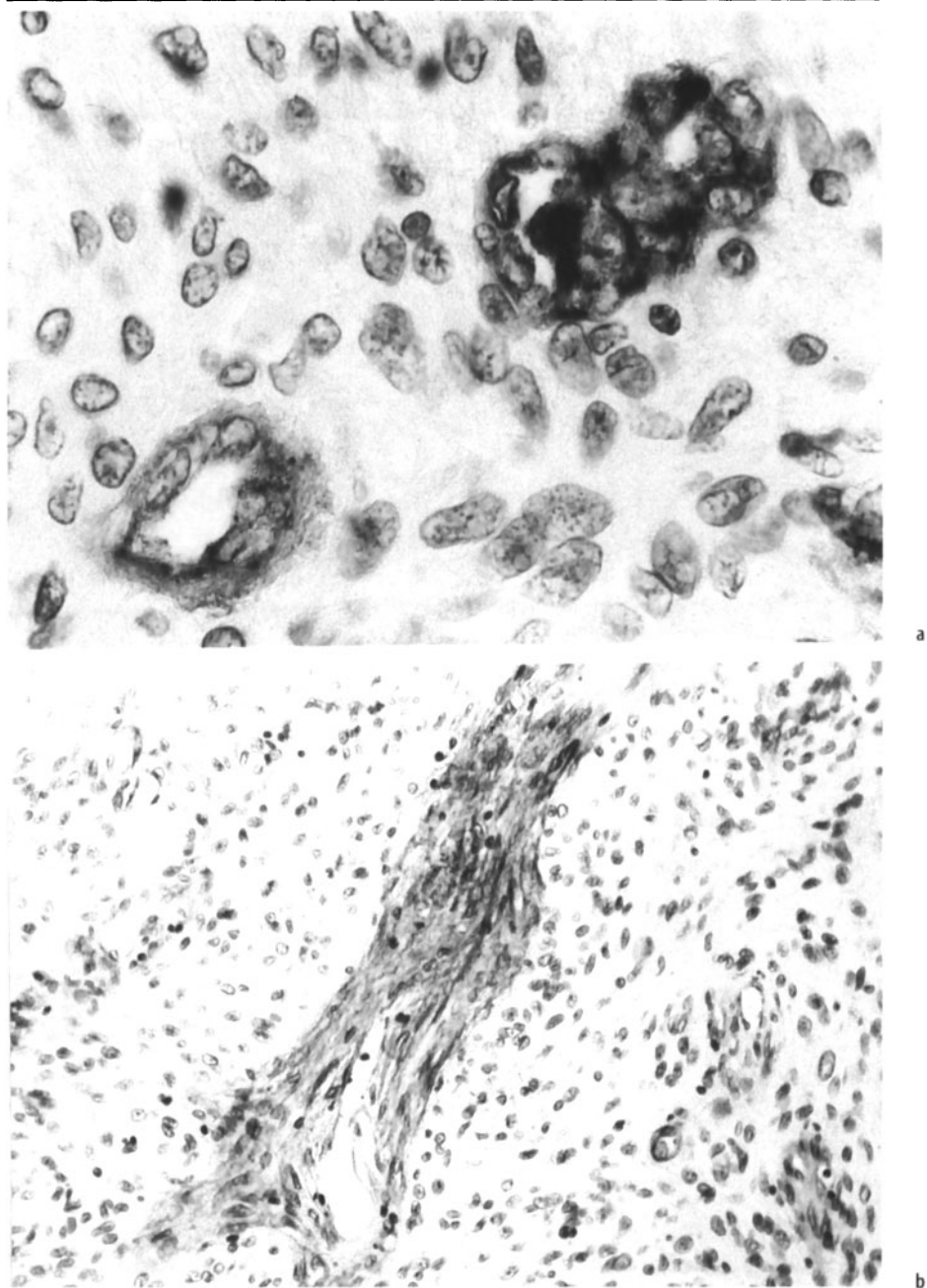
Neovascularization and endothelial proliferation are characteristic of many brain tumors, and thus the recognition of endothelial cells may be of great importance. The antigen correlated with factor VIII of coagulation (FVIII/RAG) is the most often used endothelial marker. It is one of the components of factor VIII (anti-hemophilic factor) and is produced only by endothelial cells and megacaryocytes. It is specific and widely employed in the demonstration of endothelial differentiation in many extraneurological tumors [2341].

In gliomas, the marker identifies endothelial cells of normal vessels as well as of the proliferating ones (Figs. 4.6–4.8) [3645, 2202, 2178, 3020]. It is found in Weibel–Palade bodies and in large intracytoplasmic vacuoles which discharge into the lumen (Fig. 4.7). In the glomeruli of glioblastoma, it reacts positively only in the cells lining the lumen and not in those far from it [3645]; however, by immunoelectron microscopic procedures employing colloidal gold, it has also been found in Weibel–Palade bodies of cells which do not line the lumen (see Fig. 9.33) [2261].

There are some other endothelial markers, for example CD31, which are found in endothelial cells.

Laminin and fibronectin are of great help in the study of the vasculature of tumors. Laminin is a glycoprotein occurring only in basal lamina. In the CNS, it can be demonstrated only around vessels (Fig. 4.8a) or between neuropil and pial membrane [1079]. In gliomas, antibodies to laminin demonstrate thickened and pluristratified basal membranes in and around endothelial proliferations. An inner, thickened membrane appears to be separated by the vessel wall from an outer, often interrupted membrane, in turn separating the vessels from the neuropil [1079] (Fig. 4.8b).

Fibronectin is a protein widely distributed in connective tissue, demonstrable not only in basal membranes but also in the CNS vessel walls. Even though its positivity in astrocytic cells in culture has been shown repeatedly, it is not positive in astrocytes in histological sections. In gliosarcomas, the mesodermal component is diffusely positive for fibronectin (Fig. 4.6b), thus being differentiated from the glial one, which is GFAP-positive [3020].



**Fig. 4.6.** a Positive reaction for factor VIII/RAg in hyperplastic endothelial cells in a malignant glioma. PAP-DAB,  $\times 1000$ . b Fibronectin-positive reaction in the mesodermal component of gliosarcoma. PAP-DAB,  $\times 200$

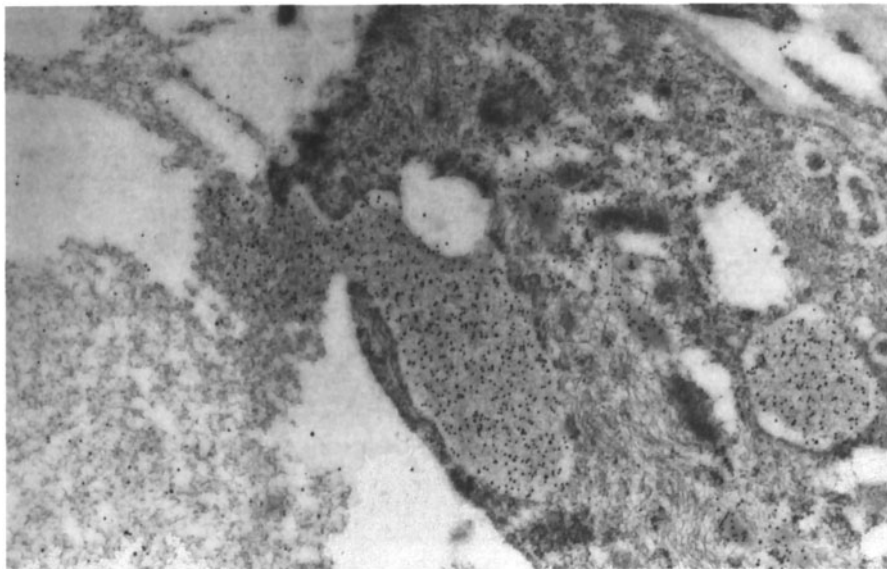


Fig. 4.7. Immunogold staining for factor VIII/RAg in a large cytoplasmic vacuole of an endothelial cell discharging into the lumen,  $\times 24\,000$

#### 4.2.5

##### Other Intermediate Filaments

Vimentin is a protein of 57 kDa; it is the first IF to appear in the course of development, regardless of the cytotype. In adult cells, it is usually replaced by the IF characteristic of each cell type; however, it remains the only IF of endothelial cells, fibroblasts, macrophages, chondrocytes and lymphoid cells. In some cell types, vimentin coexists with another IF. In the CNS, this coexpression occurs in astrocytes and tanyocytes which contain concurrently vimentin and GFAP or cytokeratin [3066, 2723]. During development, the appearance of vimentin precedes that of GFAP in astrocytes [638, 3066, 870]. In normal glia, it is weakly positive, but in reactive astrocytes it is intensely positive (Fig. 4.9b) [3022, 3023]. Vimentin is demonstrable in gliomas in both endothelial (Fig. 4.9a) and tumor cells, where it distributes like GFAP [1309, 3022]. Its occurrence, therefore, cannot be considered as a sign of immaturity in gliomas: the cells should be immature for the occurrence of vimentin and differentiated for that of GFAP at the same time. Meningioma and neurinoma cells are also intensely positive for vimentin [2723, 2005, 3022]. The same is true for stromal cells of hemangioblastomas [3022] and chordoma cells [2259].

Since most carcinomas contain cytokeratin, independent of the degree of differentiation [298], antibodies to it can be used to recognize carcinoma metastases (even undifferentiated) in the CNS. Also cells of epithelial origin, such as those of cranio-pharyngioma, dermoid and epidermoid cysts, and teratomas may similarly be recognized (Fig. 4.10). Positive staining for cytokeratin may also be observed in meningio-

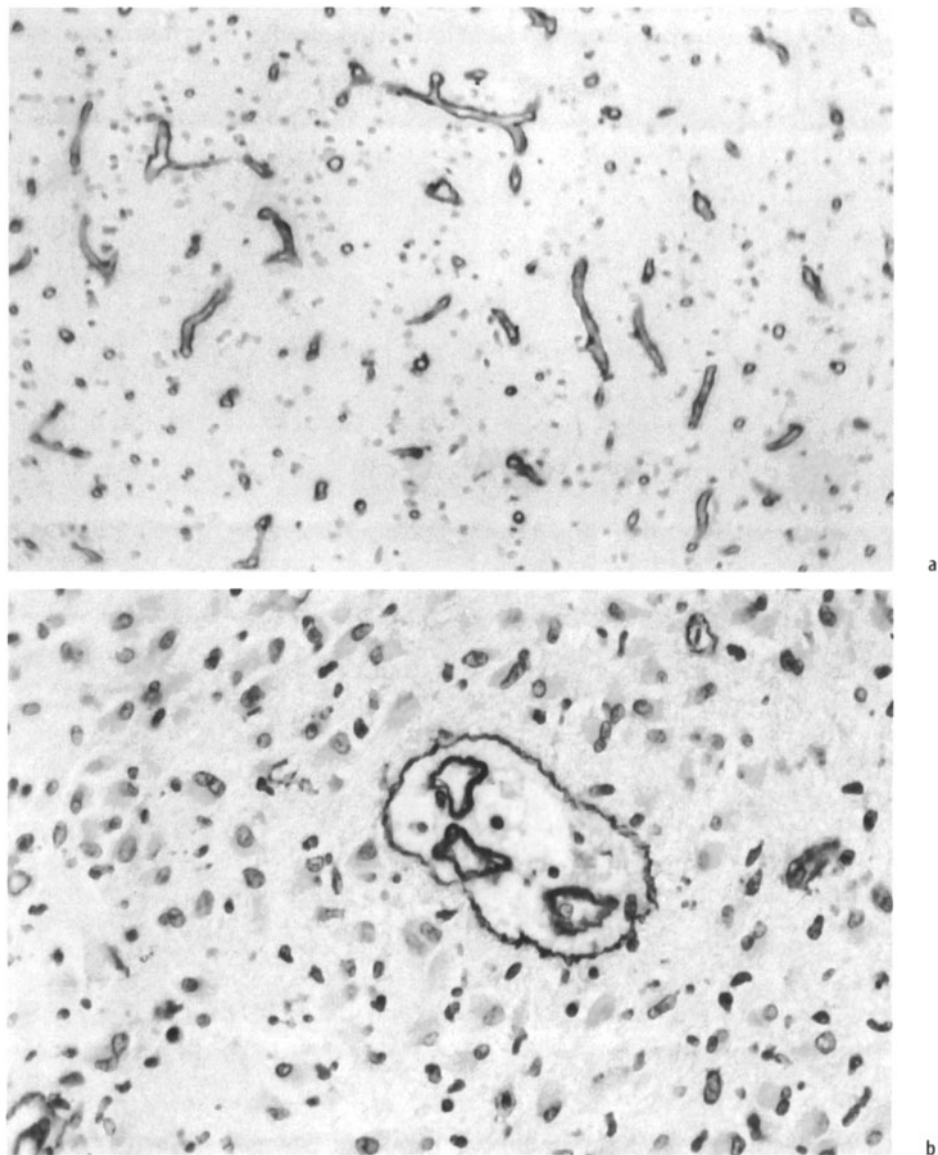
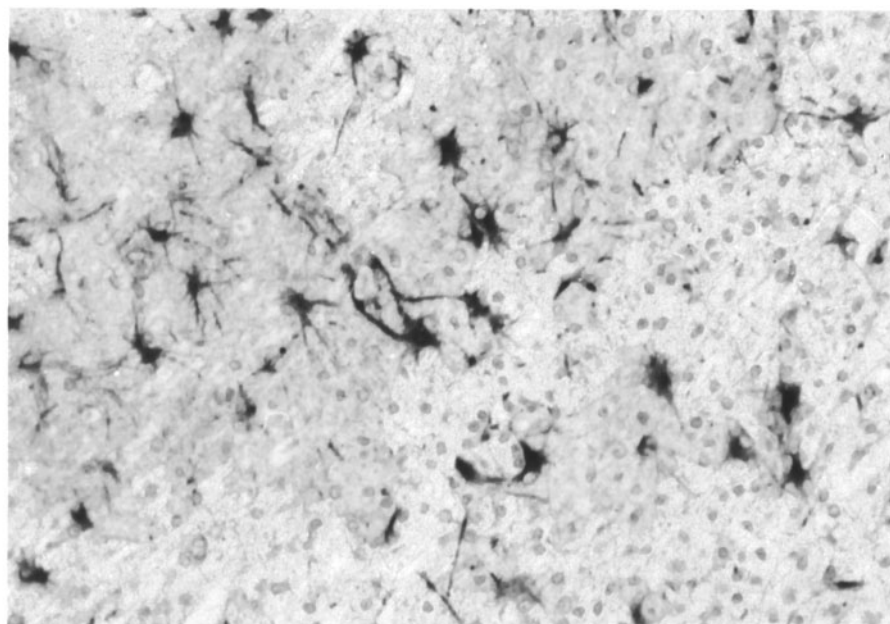


Fig. 4.8a,b. Laminin-positive reaction. a Basement membrane of capillaries in the normal cortex. PAP-DAB,  $\times 300$ . b Inner and outer membranes of the vessel wall in gliomas. PAP-DAB,  $\times 400$ . (From [1079])

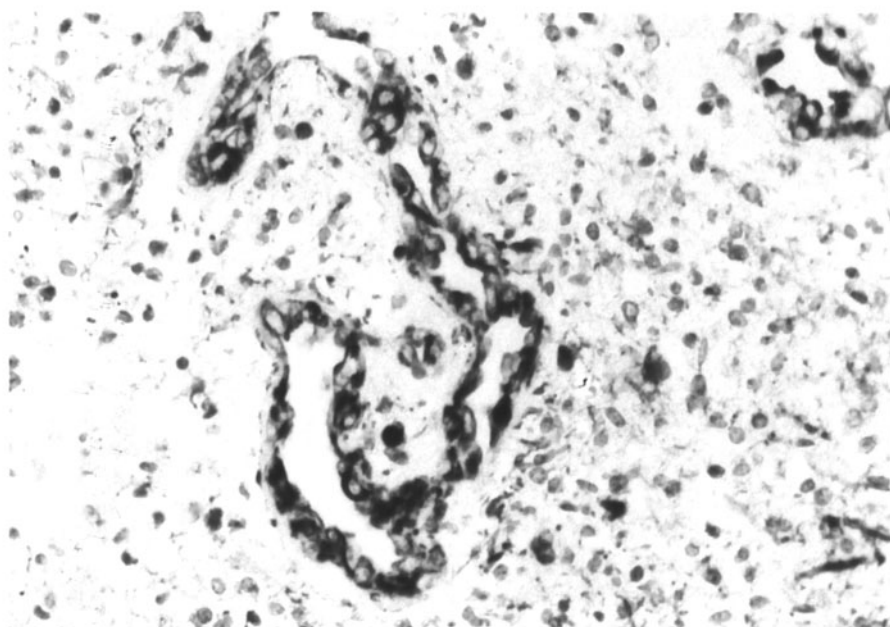
mas [2228, 3416, 1374] and in epithelial-like foci of glioblastomas and gliosarcomas [2331].

The usefulness of desmin, the IF typical of muscle cells, is limited in the tumor pathology of the CNS because it occurs only in the very rare rhabdomyosarcomas [2259].





a



b

Fig. 4.9a,b. Positive reaction for vimentin in a hyperplastic endothelial cells in a glioma and b peritumoral reactive astrocytes. PAP-DAB, 400

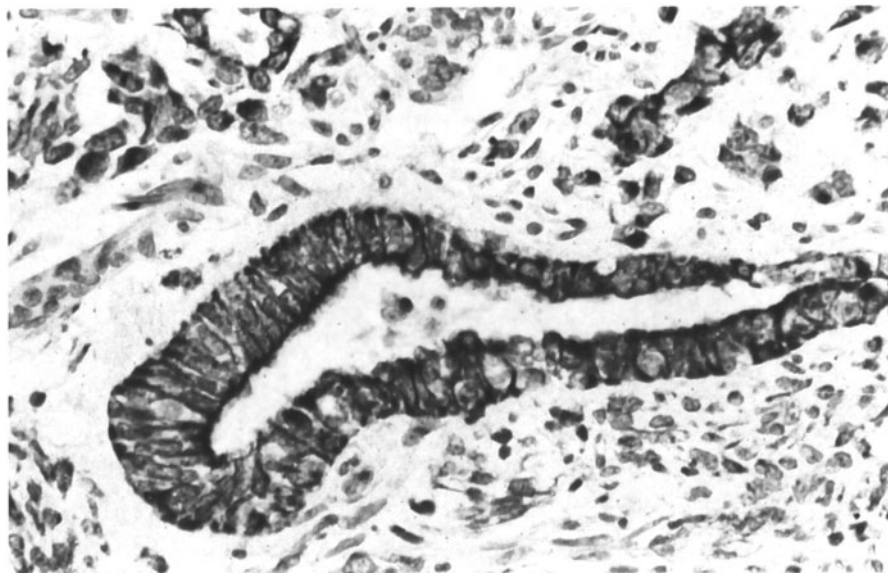


Fig. 4.10. Positive reaction for cytokeratin in epithelial cells of a teratoma. PAP-DAB,  $\times 300$

#### 4.2.6

##### Epithelial Membrane Antigens

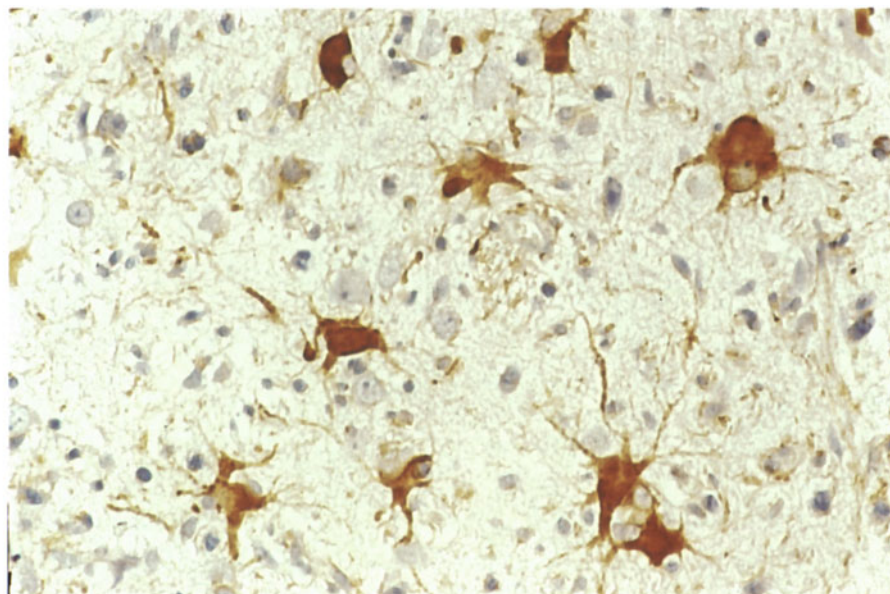
Epithelial membrane antigen (EMA) is a membrane glycoprotein occurring in most normal and tumor epithelial cells. Positive staining for it is characteristic of a carcinomatous metastasis, but it may also be observed in meningiomas [2228, 3062, 3416] and in epithelial-like structures of glioblastomas [2331].

Two other markers need to be mentioned,  $\alpha$ -fetoprotein (AFP) and human chorionic gonadotropin (HCG), which are specific for germ cell tumors. AFP is usually not found in pure germinomas [1825] but stains positively in embryonal carcinomas and endodermal sinus tumors [3759, 2455, 1825]. HCG has been demonstrated in choriocarcinomas and in trophoblasts occurring in tumors mixed with germ cells [2455].

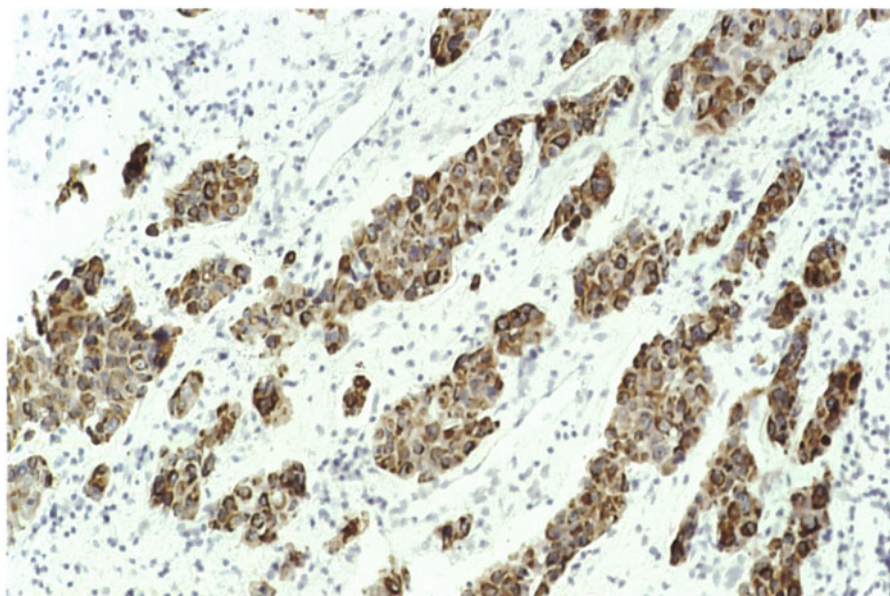
#### 4.2.7

##### Markers for Cerebral Metastases

Markers specific for the site of origin of the tumor have been established for thyroid carcinoma (thyroglobulin) [344] and prostatic adenocarcinoma (prostate-specific antigen, PSA) [44]. The markers currently available for the diagnosis of melanocytic neoplasms include polyclonal antibodies S-100 protein and NSE and mAb vimentin and NK1/C3 and HMB45 [2508]. The latter represents a highly selective antibody for the diagnosis of malignant melanoma [3212]; it is recommended for the diagnosis of



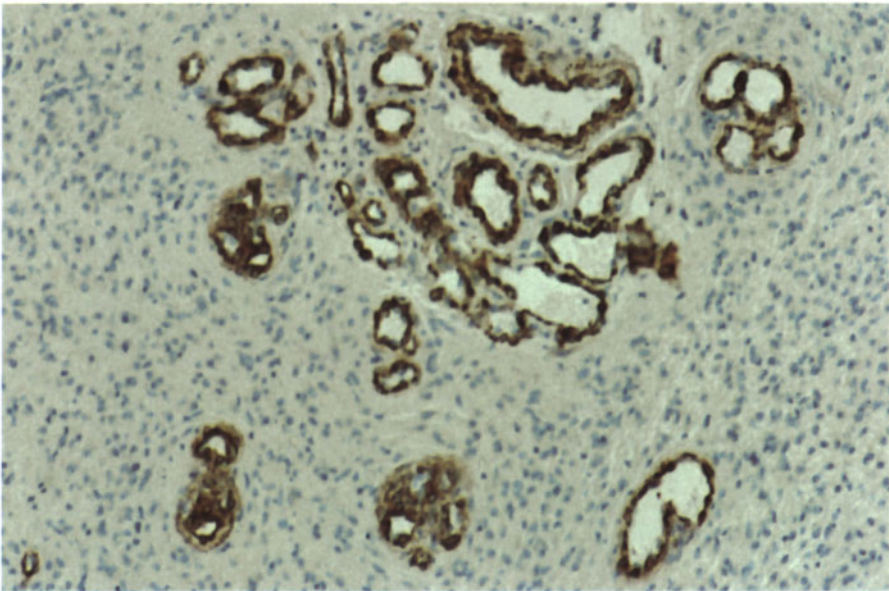
a



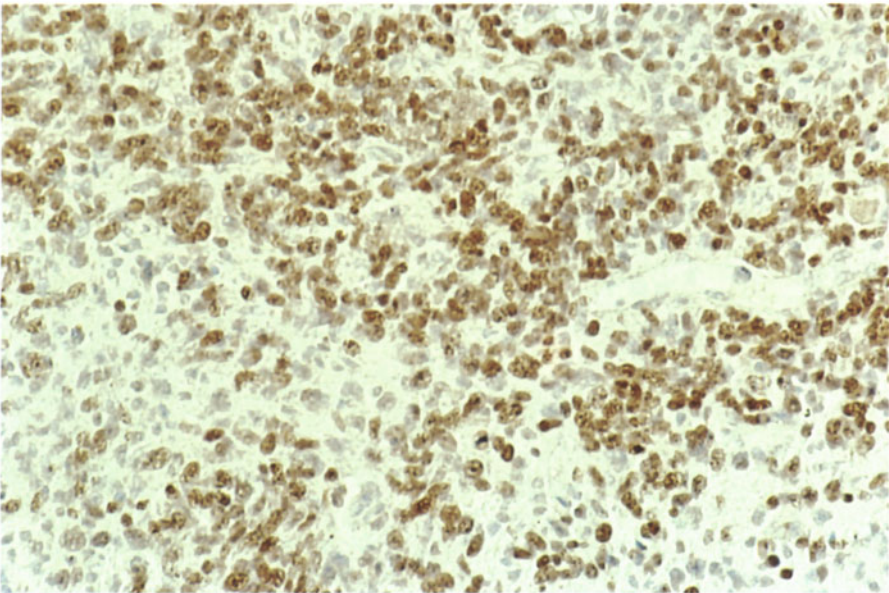
b

**Fig. 4.11. a** Glial fibrillary acidic protein (GFAP)-positive reactive astrocytes. PAP-DAB,  $\times 400$ . **b** Carcinomatous metastasis, cytokeratin-positive cells. PAP-DAB,  $\times 200$ . **c** Glioblastoma, vascular hyperplasia, a-sm-actin-positive cells. PAP-DAB,  $\times 200$ . **d** Glioblastoma, p53-positive nuclei. PAP-DAB,  $\times 200$





c



d

Fig. 4.11c, d. Legend see p. 72

cerebral metastases, because it is not expressed by cells of the nervous tissue, in contrast to the other melanocytic markers.

Panels of cytokeratin mAb (Fig. 4.11b) [2241] and of mAb expressed by carcinomas of various organs [572] are tested in order to assess specific immunohistochemical patterns of solitary brain metastases of different origin.

## Pathology of the Host-Tumor Interaction

### 5.1

#### Peritumoral Changes

##### 5.1.1

##### Glial Reaction

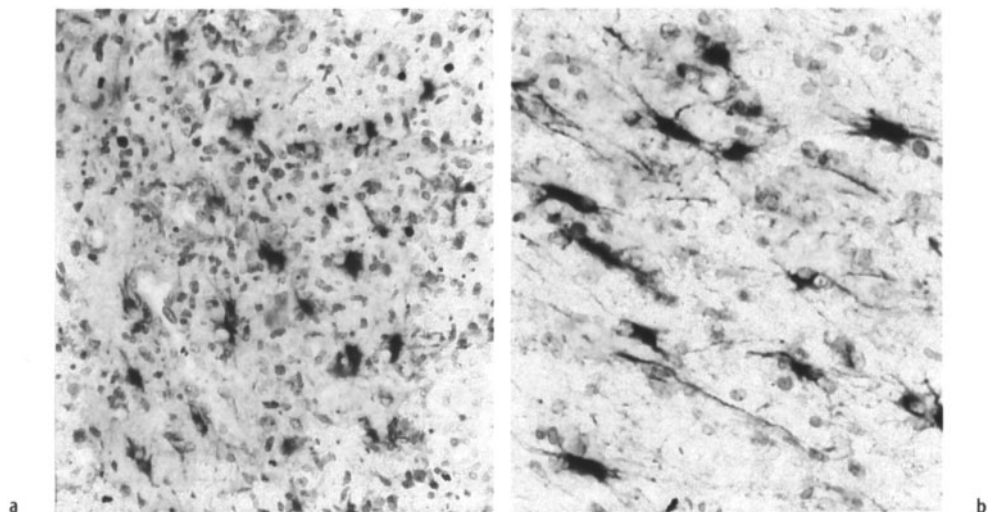
Peritumoral tissue changes are related to various factors, e.g., edema, anoxia due either to edema or compressive action of the tumor, the release of substances from the destruction of tumor cells. The most important change is glial reaction. This is a progressive or progressive-regressive process, the intensity of which varies in relation to a large number of events. The main aspect is the appearance of reactive astrocytes, either with much cytoplasm and short processes (Fig. 5.1a) or with thick and long processes (Fig. 5.1b). They are found in the peripheral parts of the tumor, in the immediate peritumoral area, or even at a distance. The first is typical of invasive tumors, whereas the latter two are typical of sharply delimited tumors.

Hypertrophic reactive astrocytes are easily recognizable with silver impregnation techniques (Fig. 5.2) and by their intense glial fibrillary acidic protein (GFAP) reactivity. They are also positive for vimentin. The less recent literature described them as strongly positive for oxidative enzymatic activities [964, 2997, 2884] with all the importance that such high metabolic activity could have (Fig. 5.3). Also, hydrolytic enzyme activities, acid phosphatase, and nonspecific esterases are evident, with different biological implications [3006].

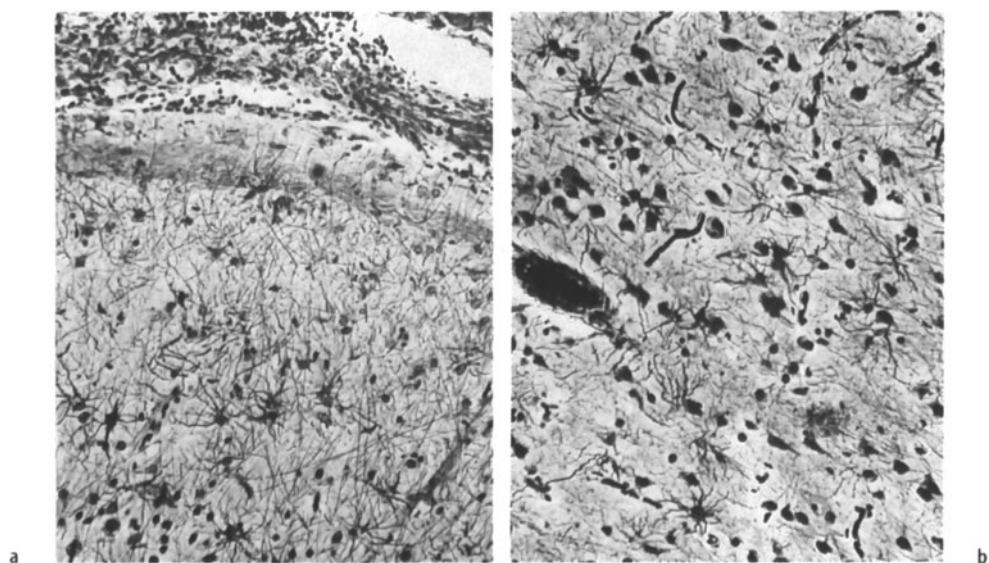
The appearance and distribution of reactive astrocytes varies depending on whether the glial reaction occurs in the white matter, in the cortex, or in the first cortical layer and on whether recent necrosis with macrophage infiltrates is present.

Reactive glia which has remained included in the tumor, or became reactive thereafter, is of special interest because in oncotypes such as medulloblastomas, oligodendrogliomas, and ependymomas it has led to endless discussions regarding its real nature, i.e., neoplastic differentiation or reactive glia. In other oncotypes, such as those of the astrocytic series, the problem is more complicated, because of the real difficulty in distinguishing tumoral from reactive glia. This is especially true in peripheral parts of the tumor (Fig. 5.4a) even when mitoses are present, for they may be seen in GFAP-positive reactive glia [3027]. The development of peritumor reactive gliosis poses a series of biological problems which have yet to be fully resolved although they have been studied by many experimental investigators.

The glial reaction is accomplished through processes of hyperplasia, hypertrophy, and lengthening of cellular prolongations. Hyperplasia occurs through mitotic divi-



**Fig. 5.1a,b.** Glial fibrillary acidic protein (GFAP)-positive staining in **a** reactive astrocytes in the periphery of a glioma and **b** hypertrophic reactive astrocytes in peritumoral white matter. PAP-DAB,  $\times 300$ . (From [2991])



**Fig. 5.2a,b.** Hypertrophic reactive astrocytes in **a** the molecular layer and **b** the middle layers of the cortex. (From [2994]). Hortega silver carbonate,  $\times 400$

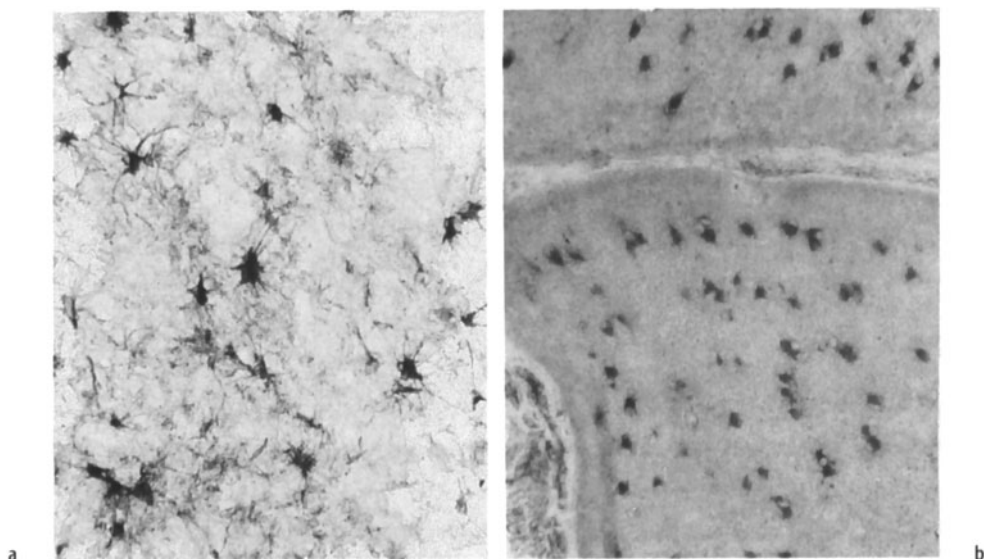
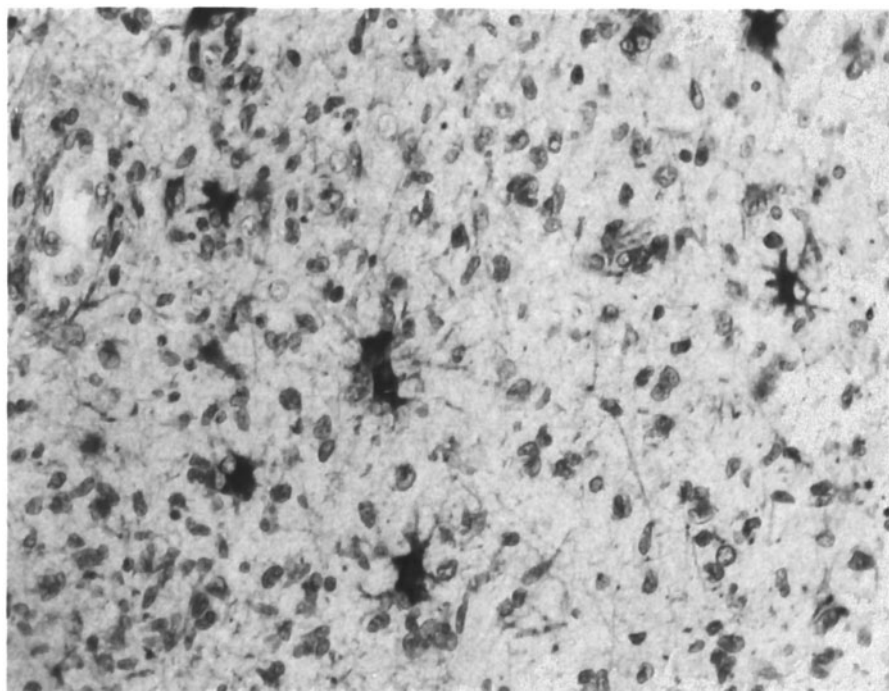


Fig. 5.3a,b. Hypertrophic reactive astrocytes in **a** the white matter and **b** the molecular layer of the cortex.(From [2994]). NADH tetrazolium reductase,  $\times 400$

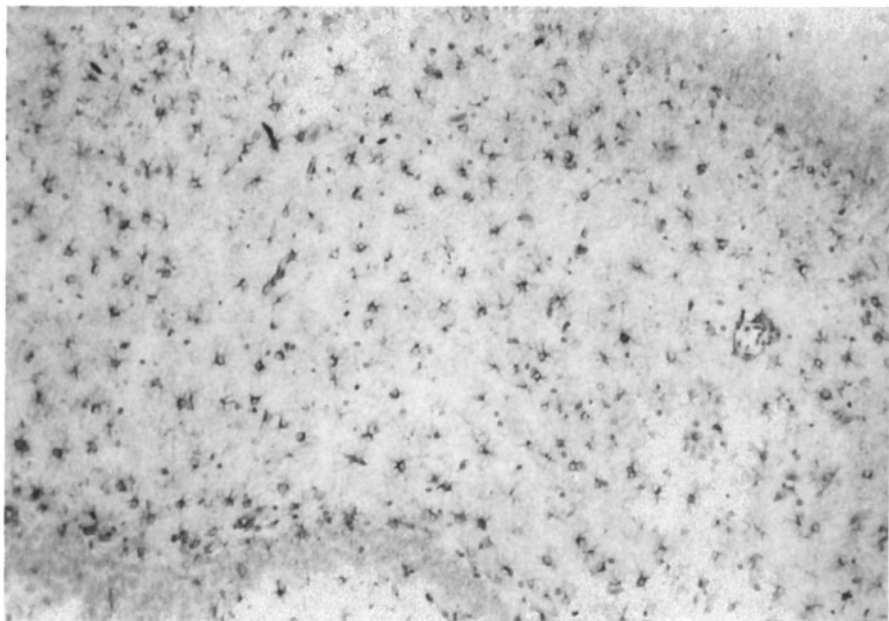
sion [455]. The responsible factors have been identified in the degeneration of neurons [162], increase of extracellular spaces [559], disaggregation of myelin [2513], ionic imbalance [353], influence of serum proteins [1695], and possibly release of gliogenetic factors [781]. Many experimental data demonstrate that the glial reaction is directed towards the pathogenic noxa and that it is stereotyped and unidirectional [826].

In light of what has been discussed in Chap. 1, it may be said that in the adult, new astrocytes must derive from cells which have maintained the ability to proliferate [3529], independent of their localization in the subependymal zone or in situ. It is known that the capacity to proliferate is maintained along with that to express GFAP [1881].

In experimental models, the occurrence of necrosis has an important influence on the distribution of the glial reaction. In general, if there is necrosis with death of neurons, the astrocytic response is hyperplastic, not only hypertrophic. In experimental models, if there is necrosis the glial response may be extensive [237, 2038, 2149]. This may be due either to the spread of the edema [876] or the peculiar distribution of astrocytes in animals. The hippocampus and the corpus callosum are, for example, the structures most affected in the rat (Fig. 5.4b) [3023]. An important finding is that, close to the lesion, astrocytes are not only GFAP positive but also strongly vimentin positive (Fig. 5.5) [2651]. Considering the significance of vimentin in cytotgenesis, this could demonstrate that they are hyperplastic, and not only hypertrophic [3023], mobile [2005], or derived from astroblasts [871]. An alternative to the origin of reactive astrocytes from preexisting astrocytes [2399] is the hypothesis that they may derive from precursor cells [871, 2274].



a



b

**Fig. 5.4.** **a** Peripheral area of a glioblastoma. Large glial fibrillary acidic protein (GFAP)-positive astrocytes of a reactive or neoplastic nature. (From [3027]). PAP-DAB,  $\times 400$ . **b** Extensive GFAP-positive gliosis in rat hippocampus following a lesion in the cortex. (From [3023]). PAP-DAB,  $\times 200$



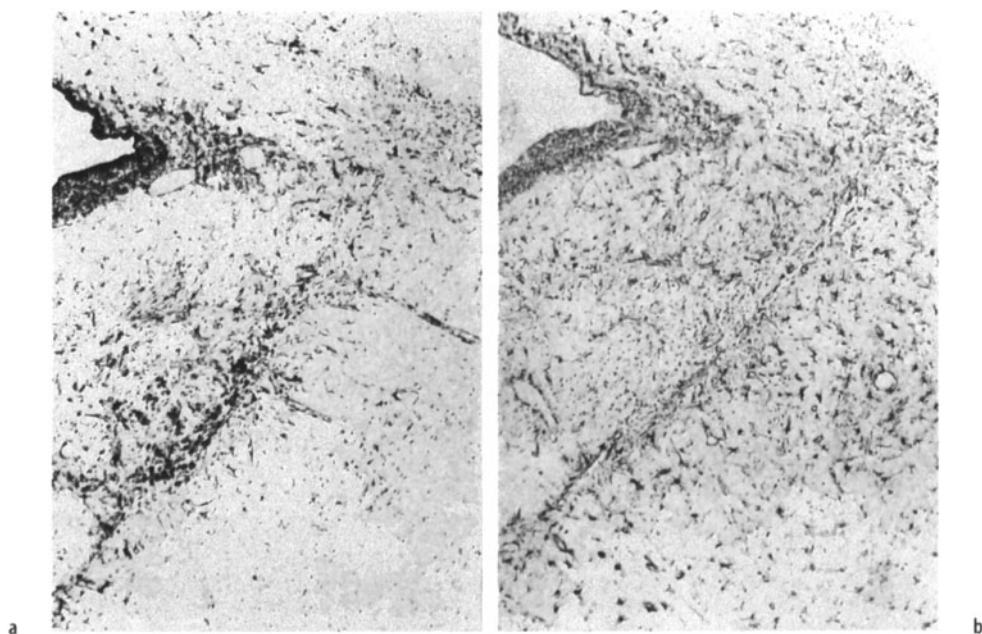


Fig. 5.5a,b. Experimental reactive gliosis in the rat. Reactive astrocytes are positive for a vimentin around a necrotic lesion and b glial fibrillary acidic protein (GFAP) at a distance. PAP-DAB,  $\times 200$

Reactive astrocytes usually do not proliferate but they can do it, as has been demonstrated in many experiments, mostly with traumatic injuries [2272, 1881, 3023, 3377, 3036]. Astrocytes near the lesion proliferate for few days and are GFAP and vimentin positive; those distant from the lesion develop through simple hypertrophy and are GFAP positive only.

Reactive astrocytes share with glioma cells the capacity to express tyrosine kinase receptors, encoded by *neu* (*erbB2/HER-2*) and *kit* genes. The two genes thus regulate cell proliferation in both cell types. Since these receptors can be demonstrated in reactive glia cells even without demonstrable mitotic activity, other receptor-mediated functions may also be relevant [1781]. The activation of these genes is not constitutive in normal astrocytes, but many environmental factors, such as catecholamines, cytokines, and lipopolysaccharides, can modify protein-synthetic activity.

It must be reminded that the expression of GFAP may increase in astrocytes without an increase in their number [3131]; conversely, astrocytes already expressing GFAP can undergo mitosis or express proliferation markers bromodeoxyuridine (BrdU) or proliferating cell nuclear antigen (PCNA).

A very important question is how a gliosis can be realized at a distance from a lesion. It is a matter of debate whether the lesion has to be traumatic or characterized by loss of substance in order to elicit a glial reaction. Most evidence indicates brain edema as the most important event; the increase of intercellular  $K^+$  released from damaged neurons seems to play a fundamental role. The swelling of astrocytes might be the main stimulus to proliferate, and proliferation might in turn be stimulated by  $K^+$  increase.

It is usually accepted that if the blood–brain barrier (BBB) is not broken, there is no astrocytic proliferation; however, it has been demonstrated that GFAP can increase even without any tissue injury and that astrocytes may respond to pathological signals in the absence of other pathological changes. GFAP may even increase in physiologic conditions and states of neuronal activity [1767, 3312]. When astrocytes respond at a distance from the lesion, signals travel through extracellular pathways or gap junctions. In vitro, a series of factors have been demonstrated to produce reactive astrocytes [2453].

Both in the reactive astrocytes in situ and in those induced in vitro with cAMP, a 48-kDa protein with a distribution similar to GFAP is associated with IF. This protein, which is present in normal astrocytes, could be responsible for the aggregation of the filaments within the processes by cross-linking and, therefore, for the formation of the processes [100].

On the basis of autoradiographic and electron microscopy findings, the hypothesis has been put forward that in traumatic lesions, and not only around them, there is a proliferative response of the oligodendrocytes [2038].

### 5.1.2

#### Included Neurons

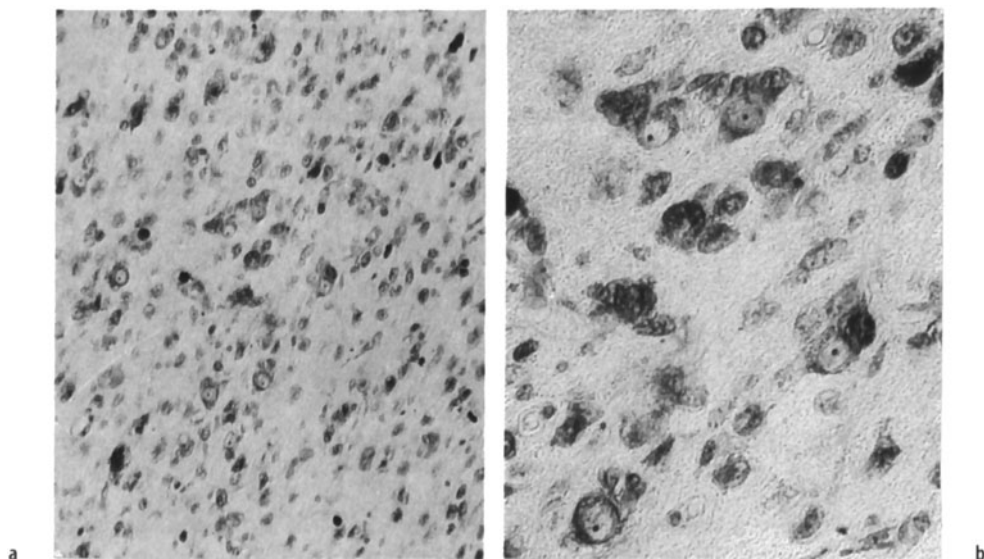
Tumor growth often spares or encompasses neural structures, leaving them recognizable for a long time. The cortex may be totally invaded but its gross structure maintained, and neurons may be recognizable even within the depth of the tumor (Fig. 5.6). They may be well preserved and remain recognizable by the presence of Nissl's granules, lipofuscin, and enzyme activities or by immunohistochemical markers. They may also show signs of atrophy, progressing to disappearance. This, in the main, is the destiny of included neurons.

In some tumors, namely in those susceptible to showing neuronal differentiation, included neurons may be the source of mistakes or contribute to fuelling the discussion regarding the problem of cellular differentiation. This is especially important in tumors such as medulloblastoma, or those of ascertained or supposed neuronal origin, in which the finding may be “expected” on the basis of a preconceived nosographic concept.

### 5.1.3

#### Ventricular Walls

During growth, the tumor may reach the ventricular walls. Two different possibilities can be entertained: the tumor may cross the subependymal layers and abut upon the ventricle, or these layers may arrest the tumor. In this latter case, the tumor gradually merges with a zone featuring intense glial reaction, not infrequently containing monstrous cells, which do not necessarily belong to the tumor. They may well be reactive cells, such as those forming subependymal gliosis with broad fiber bundles. The ependymal lining may remain intact or be destroyed or engulfed by the tumor. When the subependymal glial reaction takes a chronic course, Rosenthal's fibers may form



**Fig. 5.6a,b.** Neurons are recognizable in the cortex completely invaded by a glioma. (From [2994]). H&E, a  $\times 200$ , b  $\times 400$

even if the tumor is nonastrocytic as, for example, in oligodendroglioma, cranio-pharyngioma, and hemangioblastoma, because these fibers originated from reactive subependymal spongioblasts. A frequent event is the precipitation of pseudo-Ca/Ca in peritumoral tissue.

## 5.2

### Regressive Events in the Tumor

Regressive processes may alter the morphology of a tumor so profoundly as to modify its primary architecture and render it unrecognizable. However, both the type and degree of regressive events may be of diagnostic value. This is useful when the pathologist is given minute tissue fragments for diagnosis.

Necrosis is, without a doubt, the regressive event of major importance. Three types may be distinguished: (1) large, usually with a coagulative appearance and situated at the center of the tumor (Fig. 5.7); (2) circumscribed, with pseudo-palisading (Fig. 5.8a); (3) small, with or without pseudo-palisading (Fig. 5.8 b).

The first type (large) may be the consequence of thromboses, with occlusion of blood vessels or insufficient blood supply to the central part of the tumor due to the excessive growth.

The second type (circumscribed) is found at the periphery of large areas of necrosis, and mainly towards meninges and vascular walls. The pseudo-palisading can be regarded as a result of crowding of tumor cells, due to obstacles in their infiltrative displacement or to excessive proliferation.

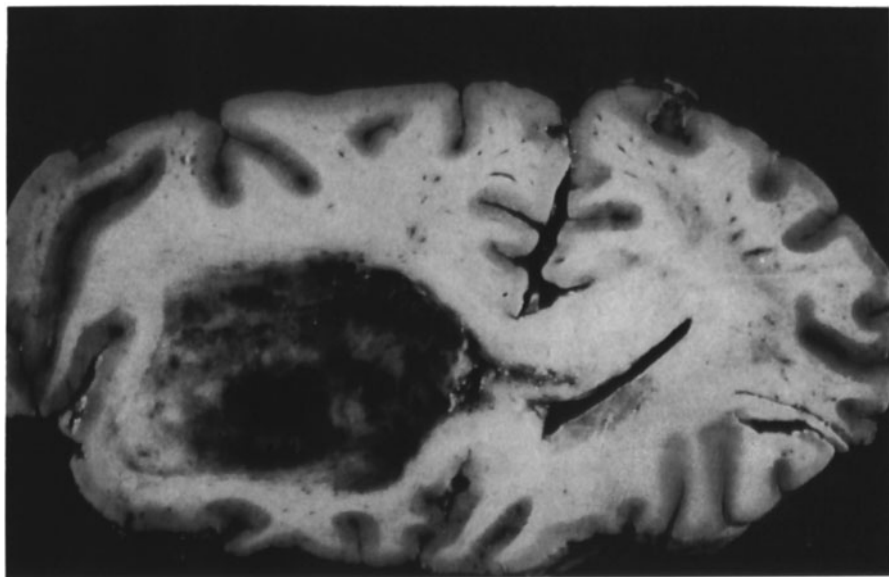


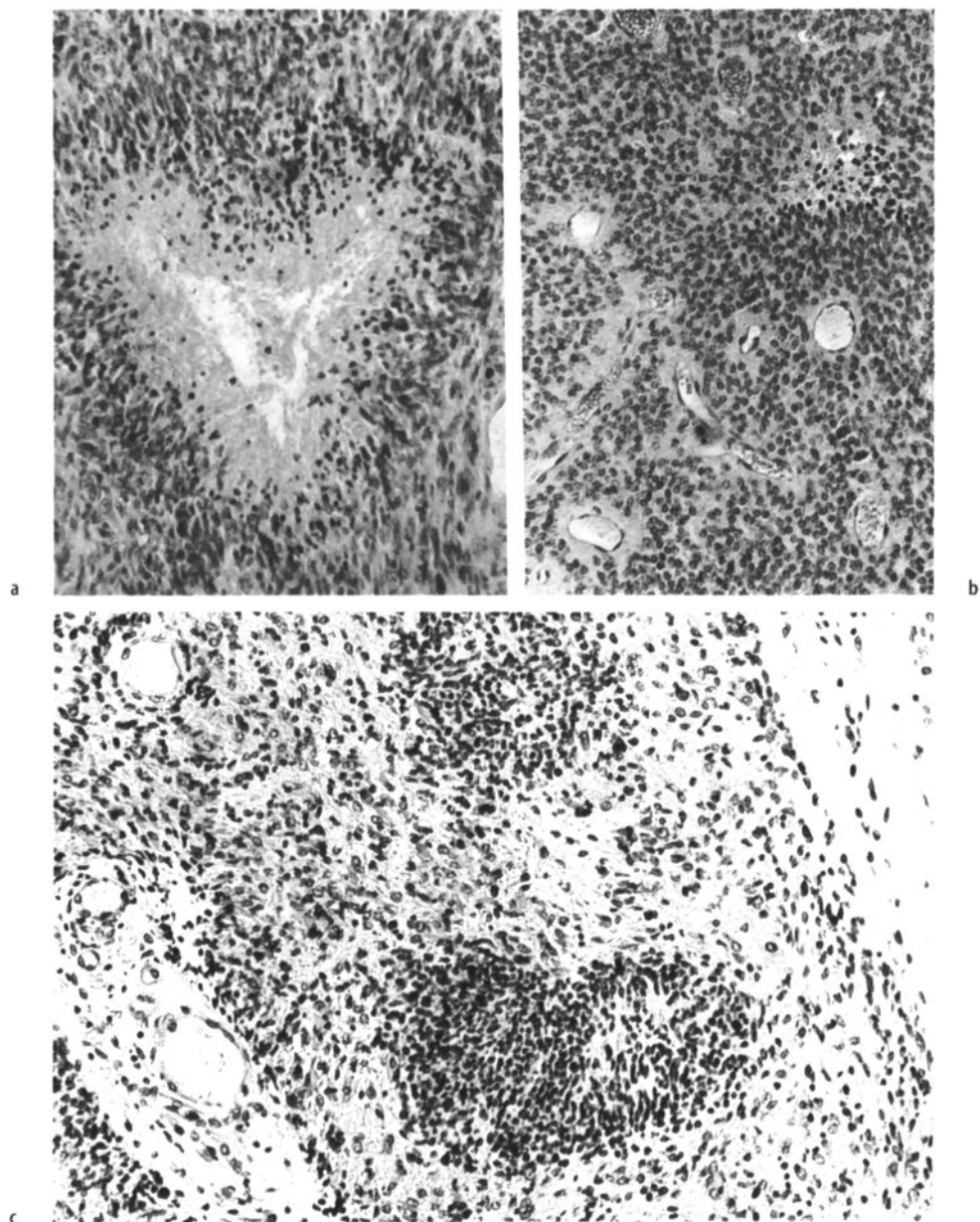
Fig. 5.7. Large central necrosis in a glioblastoma

Small necroses with pseudo-palisading usually occur in areas with very high cell density and many mitoses. A mitotic imbalance between endothelial and tumor cells may be the source [1173, 1407], as previously demonstrated outside the CNS [3389]. Necroses of this type are mostly and abundantly found in proliferative areas and indicate rapid growth (Fig. 5.8a,c). They may even disappear after radiotherapy, as a consequence of the temporary halting of tumor proliferation, and reappear later with tumor regrowth [3017]. The highly proliferating areas are GFAP negative and quite often form in the newly invaded tissue, where large, GFAP-positive reactive astrocytes occur. They remain randomly distributed and do not crowd around necrotic areas [3027]. Small areas of necrosis may be observed in almost all oncotypes such as oligodendroglioma and ependymoma, but in many cases they are very small (Fig. 5.8b) and sometimes limited to a few or single cells (apoptosis).

Another important regressive event is the appearance of cysts. These may be of variable dimension, from those visible macroscopically to microcysts. They may originate through necroses, various degenerative processes, or tissue liquefaction. Cysts may be rare in some tumors, such as glioblastoma, and numerous and very large in others, such as cerebellar hemangioblastoma, in which the entire tumor may be reduced to a small mural nodule and a large cyst. Microscopic cysts may, however, be present in almost all cerebral tumors.

Hemorrhages are other frequent regressive events in cerebral tumors. They may occur in all CNS tumors to a varying degree and extent and even be so massive as to assume clinical significance (e.g., apoplexy in a glioma). These massive ones occur mostly in glioblastoma, oligodendroglioma, and pituitary adenoma.

Still other regressive events are hyalinization and fat degeneration. The former occurs in connective tissue and is particularly frequent in meningiomas, but it is also



**Fig. 5.8.** a Circumscribed necrosis with pseudo-palisading in glioblastoma. b Very small necrotic focus in an ependymoma. c Glioblastoma, transformation of areas with high cell density into circumscribed necroses. H&E,  $\times 200$

found in the blood vessels of neuroepithelial tumors, especially glioblastoma. Fat degeneration is the result of a slowly evolving necrobiotic change.

## 5.3 Cerebral Edema

### 5.3.1

#### Definition and Pathogenesis

Cerebral edema is an important pathological event which occurs in association with cerebral tumors and is capable of influencing cerebral blood flow, metabolism, and intracranial hypertension. It may seriously aggravate the hypertension, if already present. Generally, three types of cerebral edema are acknowledged: vasogenic, cytotoxic, and ischemic [1696, 911, 543].

Cytotoxic edema is related to the direct effect of noxious agents on cells of the cerebral parenchyma so that neurons, glia, and endothelial cells become swollen. There is an increase in the water and sodium content in the cells because of a disturbance of the adenosine triphosphate (ATP)-dependent sodium pump. At the same time, the volume of the extracellular spaces reduces, while capillary permeability remains normal. Ischemic edema is initially cytotoxic and progresses with the development of necrosis. The BBB is subsequently damaged, so the edema becomes vasogenic. The latter accompanies tumors, inflammatory processes, and necrosis. It is due to a change in the permeability of the BBB.

The concept of BBB arises from the observation that small molecules pass freely from the blood to many tissues but poorly or not at all in to nervous tissue, as though a barrier existed. For example, in the old experiments of Ehrlich and Goldmann, trypan blue penetrated various other body tissues from the blood but not the brain, unless it was administered via the CSF. The abundant subsequent research led to four basic observations: (1) some substances, such as trypan blue and proteins, penetrate tissues from the blood vessels but not the brain; (2) some normal metabolites may increase in concentration in the blood but not in the brain; (3) the majority of substances penetrate the brain more readily via the CSF than via the blood; (4) the majority of substances penetrate the liver and kidney more rapidly than the brain.

Today, we know that trypan blue does not cross from the blood vessels into the brain because it binds to serum proteins which do not cross the BBB, and that it enters the brain via the CSF, because of the low protein concentration of the latter, which leaves it mostly unbound. The best demonstration of the existence of the BBB was given in the peroxidase experiment of Reese and Karnovsky [2737], which demonstrated that the anatomical site of the BBB is at the level of the endothelium of cerebral capillaries, which differs from that of other organs in accordance with various characteristics. First of all, the cerebral capillaries are mostly of the “continuous” type, e.g., the endothelium and the basement membrane are uninterrupted, and a true extracapillary space does not exist, as the perivascular zone is occupied by astrocytic processes. Second, the endothelial cells of cerebral capillaries have tight junctions which are “tighter” than those found in other organs. Lastly, cerebral endothelium contains fewer pinocytic vesicles [2750], as compared with the endothe-

lium of other tissues. There are, however, some areas in which the BBB does not function: the area postrema, the insertion line of the choroid plexus, the median eminence of the hypothalamus, and the pineal gland (in which the capillaries are of fenestrated type, e.g., have small openings in the wall which allow macromolecules to cross into the extravascular space).

The endothelium is, therefore, the site of the BBB, so that the brain is protected from noxious substances and biochemical homeostasis is maintained. The passage of various substances into the cerebral parenchyma is regulated by different mechanisms. First of all, the endothelium is polarized. It harbors  $\text{Na}^+$  and  $\text{K}^+$  pumps on the abluminal surface and specific receptor proteins on the luminal plasmalemma [228]. Lipid soluble and apolar substances easily cross it, whilst larger molecules and proteins do not. The BBB is, however, actively and selectively involved with respect to small molecules; for example, saccharose and inulin seem to enter the brain less easily than other tissues. It is possible that the CSF may carry out an important "wash-out" function in reducing the intracerebral concentration of these substances, apart from the obstacle represented by the tight junctions. Because the CSF is in equilibrium with the fluid in the extracellular spaces and is continuously being renewed, molecules penetrating from the blood into the extracellular cerebral spaces may rapidly pass into the CSF, thereby being quickly washed away.

A specific active transport system (a sort of "pump") is, instead, the basis of the entry into the brain of many metabolites. For example, D-glucose, mannose, and maltose, but not L-glucose, galactose or fructose, rapidly cross the BBB. The plentiful mitochondria in brain endothelial cells, in contrary to endothelial cells elsewhere in the body [2488], indicate an active transport, as this process requires a great amount of energy [911].

Other substances, such as glutamic acid, do not seem to cross the BBB, because they may increase in concentration in the blood without increasing in the brain. However, it has to be said that this could also be due to a rapid washout from the CSF. For substances such as ethanol, lipid-soluble molecules, and certain gases such as  $\text{CO}_2$ ,  $\text{O}_2$ ,  $\text{N}_2\text{O}$  and Xe, there would be no barrier impediment.

Blood-borne proteins may enter the central cerebral endothelia by fluid phase, adsorptive, and receptor-mediated endocytosis in which secondary lysosomes are involved, degrading the proteins [338]. For example, in adsorptive transcytosis of lectins, the Golgi saccules are reached and the molecules are packaged for intracellular transport and exocytosis at the abluminal surface [339]. The receptor-mediated transcytosis is highly specific and very quick.

Vasogenic edema is due to the breakdown of the BBB, resulting from damage to the endothelium. This results in an increase in vascular permeability with extravasation of serum components, including proteins, which under hydrostatic pressure diffuse into the extracellular space, first into the tumor and then around it. The modalities of this process may be multiple and changes have first to be looked for in the structure of the blood vessels.

Tumor blood vessels are frequently fenestrated, and the junctions between endothelial cells are wide. The endothelial surface is irregular, with the formation of deep folds which facilitate the passage of material through the endothelium [3585]. The endothelium of tumor blood vessels shows an increase in pinocytotic vesicles as compared with normal cerebral endothelium. In analogy to what has been observed

in other models of edema, the vesicles may form at the luminal surface of the endothelium and be transported to the opposite side, where their content may be discharged outside the endothelial cell. In other instances, because of the confluence of numerous vesicles, true channels traversing the endothelium may form [2675].

In tumor blood vessels, a true pericapillary sheath as formed by glial processes under normal conditions is lacking. It might be said that in tumors there is an absence rather than a breakdown of the BBB [2007, 2661]. Under different conditions and particularly in the acute phase of inflammatory processes, leukocytes traverse the endothelial cytoplasm or wedge themselves between two adjacent endothelial cells to reach the perivascular space by a process called "emperipolesis" [103].

The relative importance of these structural alterations of the endothelium in the genesis of tumor edema has not been completely clarified. A quantitative study in glioblastomas [560] has recently revealed the quantitative importance of the formation of canaliculi and true breaks of the endothelial layer as compared with pinocytotic vesicles and fenestrations, which could be less frequent than expected.

An important pathogenetic role in the formation of vasogenic edema is played by the products of the degradation of phospholipids of the cell membranes and of arachidonic acid, which is the main polyunsaturated fatty acid in the brain and its tumors [477]. The liberation of arachidonic acid in cerebral tumors may be capable of triggering a series of events in the capillary walls by increasing their permeability and, therefore, increasing the amount of edema [913].

The action of permeability factors has also been demonstrated in the peritumoral area. Apart from prostaglandin E and thromboxane B<sub>2</sub> [565], other factors have been identified in the supernatant of cultures of C6 glioma cells [2481] and of human gliomas [358, 597]. The factors could be inhibited by dexamethasone. On this point of view there is no general agreement, because there is no doubt about the existence of structural changes in tumor blood vessels resulting in increased permeability. The same cannot be said with certainty for the peritumoral tissue.

The majority of studies has demonstrated a lack of change in blood vessel permeability in peritumoral tissue [1695, 269]. This is analogous to what occurs in other conditions which lead to cerebral edema, where the damage to the BBB is present only at the site of the lesion and not in the surrounding edematous tissue.

A 47% reduction of capillary permeability to sodium and urea has been observed in the cerebral peritumoral tissue in the rat [1928]. The reduction could be secondary to compression by the tumor on peritumor capillaries or an accumulation of tumor metabolites which inhibit the transcapillary transport of sodium and urea.

There are, however, observations that blood vessels in peritumoral position show open junctions and more vesicles than normal, thus appearing to be leaky. Ultrastructurally, they appear to be of immature type [3644].

It is possible that the tumor infiltration per se induces the increase of vessel permeability in the invaded tissue, perhaps through diffusible factors [3315]. This hypothesis is supported by the observation that in microvessels there are many more changes in the interendothelial junctions the greater the tumor infiltration is, even when capillaries are not directly surrounded by tumor cells. Experimental brain tumors have demonstrated many of the same abnormalities as human tumors [2929].

There is no complete agreement between various authors on the electrolyte composition of the cerebral edema fluid: reduction of the sodium content and increase in



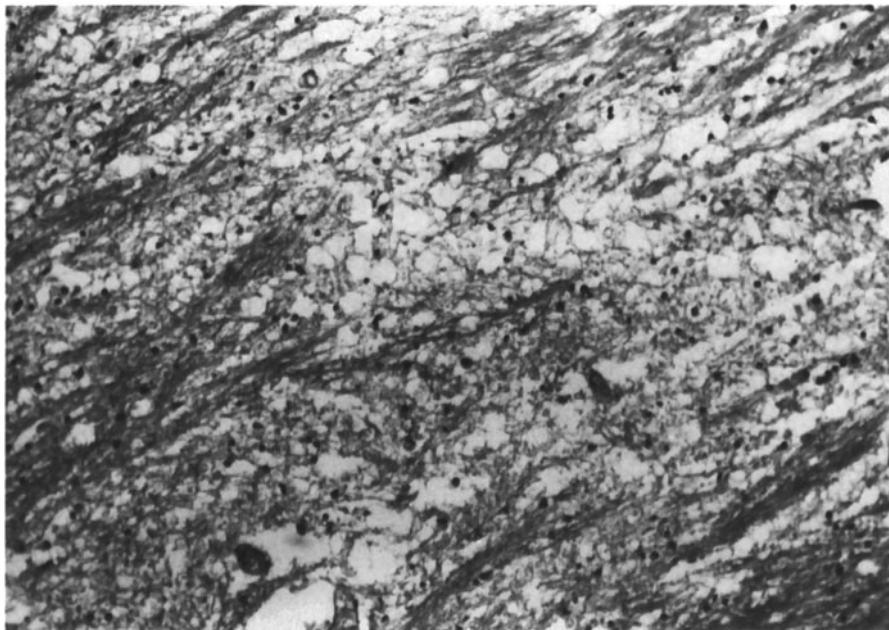


Fig. 5.9. Peritumoral edema in the white matter. Dissociation of myelin fibers and demyelination. Luxol fast blue B,  $\times 200$

potassium in the brain [2769, 1415] or the opposite [1613]. The protein content is also not identical to that in serum. In edematous white matter, for example, the increase in  $\gamma$ -globulins occurs at a later time than the increase in albumin.

### 5.3.2

#### Morphological Changes and Sequelae

The increase in fluid content causes an increase in volume and weight of the brain, which leads to flattened gyri, narrowed sulci, and small ventricles. In vasogenic edema, the edema fluid collects mainly in the extracellular spaces between the white matter fibers. Even in the earlier phases, the dilatation of this space may be demonstrated at the ultrastructural level if the tissue is properly fixed [1332]. The use of electron dense tracers allows easier detection. Under worse conditions, edema is also apparent with conventional histologic examination as vacuoles of various dimension in the white matter and as dilatations of the perivascular and perineuronal spaces and dissociation of myelin sheaths (Fig. 5.9). The preferential diffusion of the edema fluid in the white matter is due to the fact that it follows anatomical pathways of lesser resistance. The bundles of fibers in the white matter, thanks to the absence of demonstrable junctions between the myelin fibers, are easily dissociated for considerable distances and facilitate the diffusion of the edema fluid (Fig. 5.10). On the con-

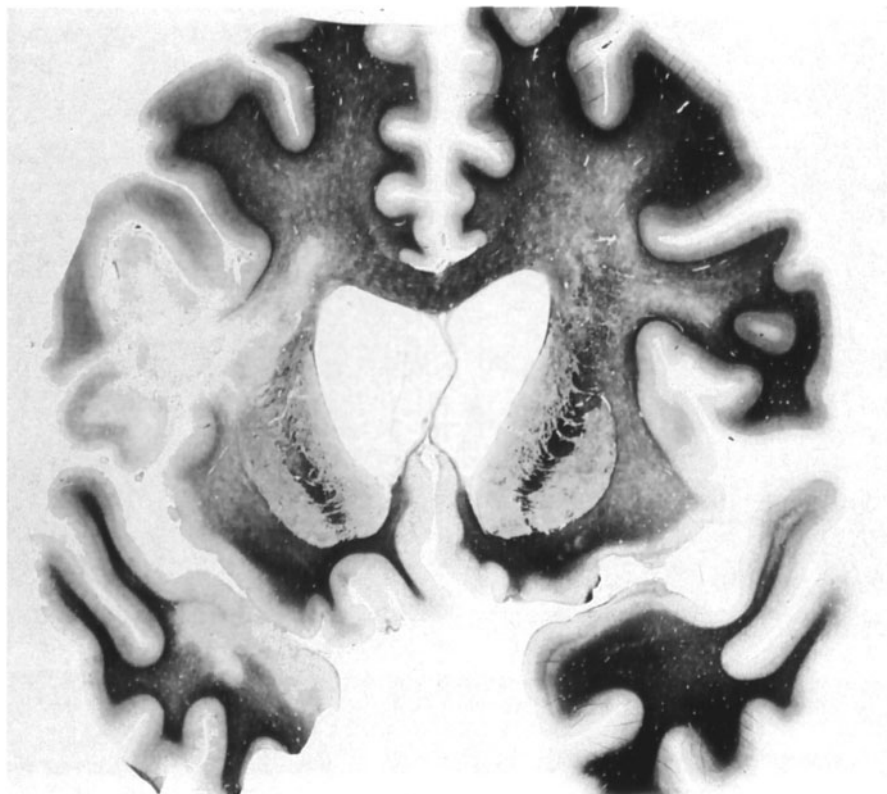


Fig. 5.10. Peritumoral edema diffused through the white matter of both hemispheres with myelin loss. Luxol fast blue B,  $\times 1$

trary, the thick network of junctions in the cortex (synapses and junctions between glial cells) remarkably limits the progression of the edema.

The progression is not simply the result of passive diffusion but is related to active pressure [2769]. In fact, there is no difference in the speed of diffusion of molecules of different size. However, the speed of edema progression at around 10 mm/week [1415], which is inferior to that expected by simple diffusion, demonstrates that the main influence is an expression of the pressure exerted by the fluid coming out of the capillaries, rather than of the resistance of the tissue [1415]. At any rate, there is a gradient in the water content of the peritumoral white matter which decreases as the distance from the tumor increases. The edema fluid, finally, is in part drained into the ventricular system when the edema front reaches the walls of the ventricles [2769]; the serum proteins are absorbed by astrocytes, macrophages, and even neurons, which transport them to the blood vessels, pia, or ependyma with a possibility of being discharged into the CSF [2737]. The persistence of the edema causes the appearance of serious tissue changes such as demyelination and reactive astrocytosis (Fig. 5.11).

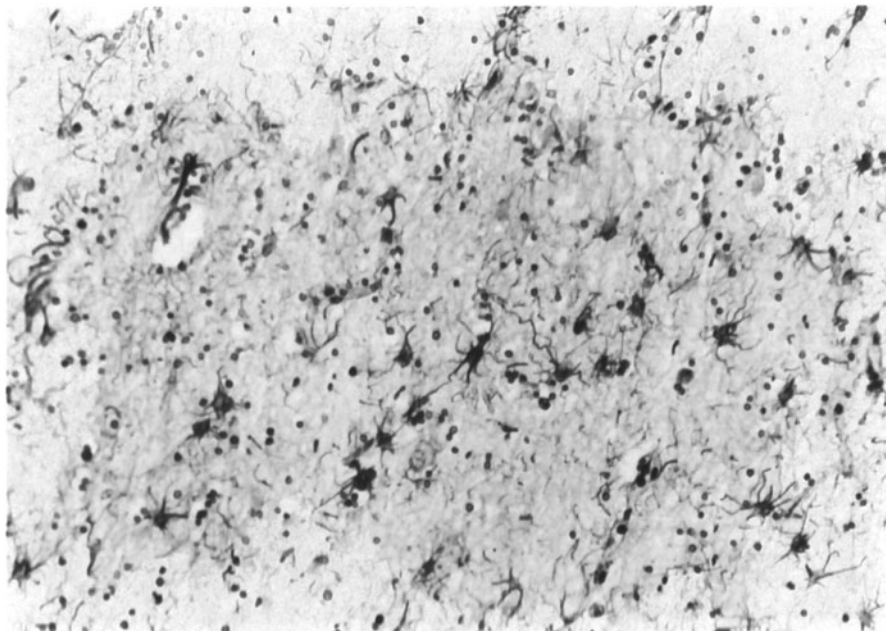
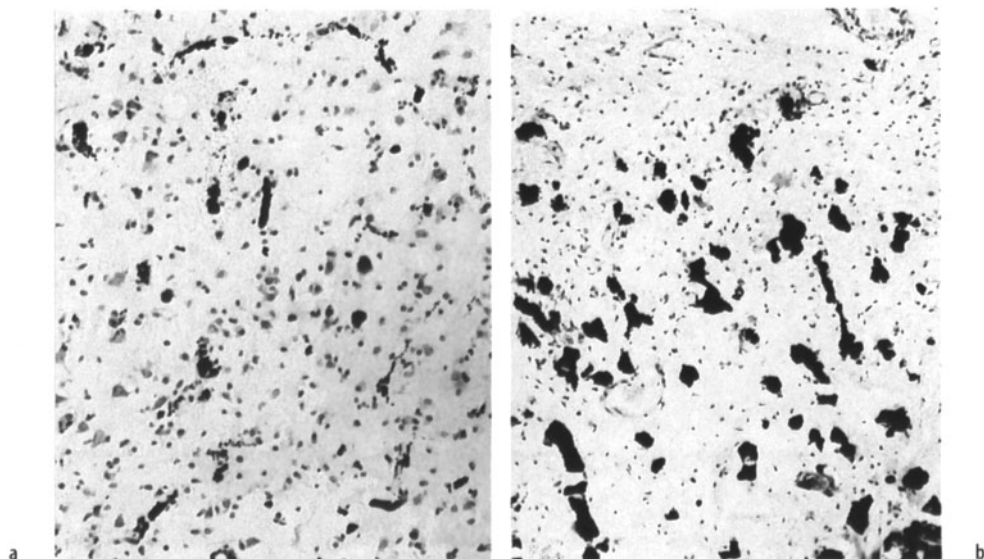


Fig. 5.11. Fibrous gliosis in chronic edema. Holzer,  $\times 300$

Cerebral edema may influence the blood vessel flow by reducing the perfusion pressure as a consequence of the increase in intracranial pressure, or by increasing vascular resistance by compressing the microcirculation [1415]. Even if there is no complete agreement between studies on tumor edema in man and under experimental conditions, it is, nevertheless, probable that cerebral edema causes a decrease in the regional blood flow [166] when it is accompanied by an increase in intracranial pressure.

Tumor-associated edema on computed tomography (CT) scan is usually seen as a hypodense area surrounding the area of tumor enhancement. On magnetic resonance imaging (MRI), it appears as a region of increased T2 signal outside the gadolinium enhanced area. When the enhancement is not present, for example in infiltrating or in low grade tumors, then it is very difficult to differentiate between infiltrated tissue and edema [705]. It must be taken into account that malignant cells can be found long distances away from the major tumor mass [2990, 1629, 389]. Steroids are effective in reducing tumor-associated edema [3123], including that associated with inflammation [910], even though the exact mechanism is not known. Since they are not effective in all types of edema, one may conclude that they are not effective in all conditions under which the BBB is altered.



**Fig. 5.12.** **a** Pseudocalcium-calcium (PCa-Ca) precipitations as fine granules on capillaries in an astrocytoma. H&E,  $\times 200$ . **b** Broad precipitations on vessel walls in an ependymoma. Cresyl violet,  $\times 150$ . (From [2994])

## 5.4 Calcifications

The old concept relating the presence of calcifications to the benign nature of a process has been surpassed and is today unacceptable. Multiple factors come into play in their production. The frequency of calcification in the different oncotypes varies greatly, being very low in some, high in others.

Calcifications may be detected by conventional radiology in a small percentage of cases; however, the percentage increases with CT [2456], even though, according to some, the majority of calcifications seen on CT are also visible on plain X-ray films [1146].

MRI is even more sensitive, and calcifications appear as areas of signal attenuation because of the lack of mobile hydrogen [326, 3791]. However, calcifications are often not seen on MRI.

From the morphological point of view, calcifications in gliomas are not dissimilar from those which are observed in the “symmetric, nonarteriosclerotic deposition of pseudo-Ca/Ca” or in other calcifying conditions [838].

Fine granules may deposit on capillaries and subsequently become confluent, so as to form strings of beads or larger structures, giving the capillary network a coral-like appearance. This type of precipitation is more frequent in peritumoral tissue, especially around oligodendrogliomas or astrocytomas (Fig. 5.12).

Precipitates may occur in the blood vessel wall both as granules, which subsequently become confluent, and as larger precipitates. The blood vessel wall may be-

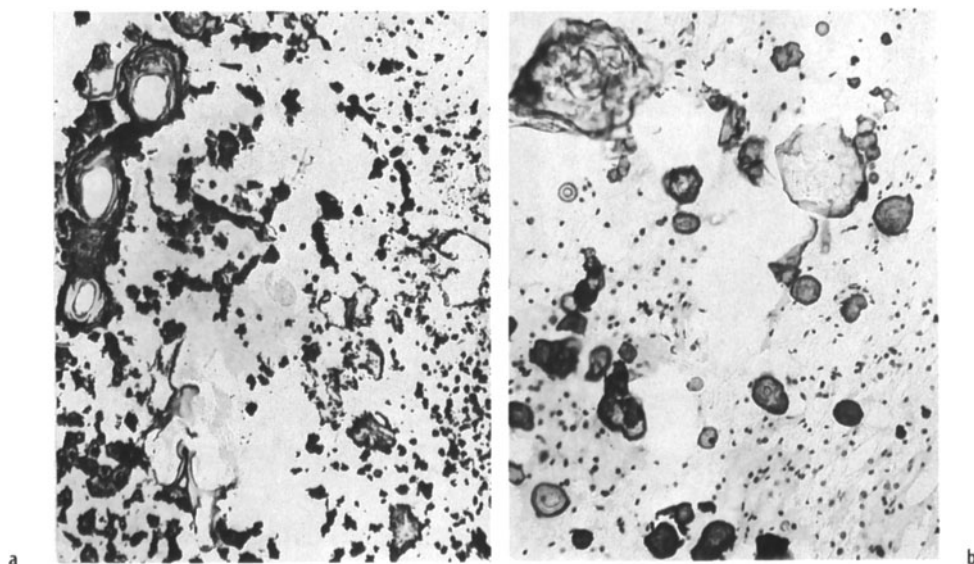


Fig. 5.13a,b. Oligodendroglioma. a Pseudocalcium-calcium (PCa-Ca) deposits on the whole vascular network. b Agatiform stratifications in large deposits. (From [2994]). Cresyl violet,  $\times 100$

come impregnated, and ring calcifications may form. This type is particularly frequent in oligodendroglioma, in which a large part of the blood vessel network may undergo changes similar to those in Sturge-Weber disease (Fig. 5.13a).

A last type is in the form of stratified, morular, and needlelike deposits, of different sizes and staining properties, apparently lying free in the tissue (Fig. 5.13b). This type appears mostly within the tumor or in infiltrated cortical areas.

Calcific deposits are basophil, stain variously with cationic dyes depending on the intensity of mineralization, are metachromatic with toluidine blue, and are negative for lipid reactions. The histochemical behavior is not dissimilar from that described in the symmetric deposits of pseudo-Ca/Ca [2988]. They are formed by an organic matrix and a mineral component. The former includes a protein-GAG complex, showing an extinction point at pH 2.6–3.1 and alcian blue positivity, as may be observed in Fahr's disease [3003, 3004]. The GAG may vary from one tumor to another or within the same tumor, depending on the stage in which the calcification occurs. This is well demonstrated with fluorochromization by acridine orange [3004].

The mineral component is very variable. Ca salts are usually demonstrated with routine histochemical methods, while the presence of iron depends mostly on the stage of evolution of the deposits and on their location in different cerebral areas. For example, the presence of iron is much easier to demonstrate in the first stages of calcification and in cerebral areas where it is normally present. In small deposits, minerals are more difficult to demonstrate than in large ones, even with the help of microchemical and microincineration methods.

Chemical analyses reveal the content of phosphates and carbonates, but the former clearly predominate [2988], as occurs in Fahr's disease, Sturge-Weber disease,

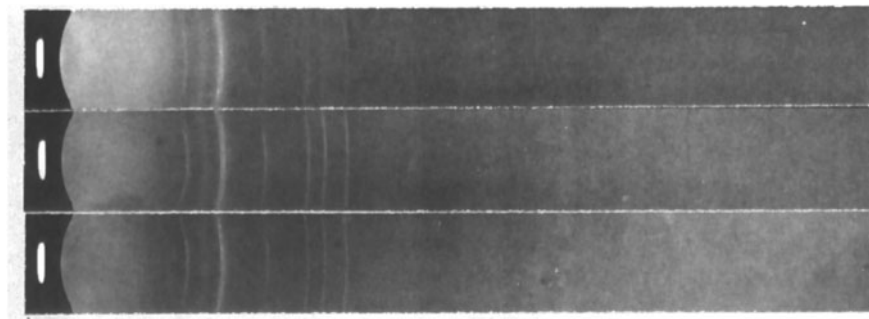


Fig. 5.14. Roentgen spectrophotographic analysis. *Top*, bone fragment in a meningioma. *Middle and bottom*, oligodendroglioma, small and large deposits, respectively. Apparatus Rx General Electrix, type XRD3. (From [3001])

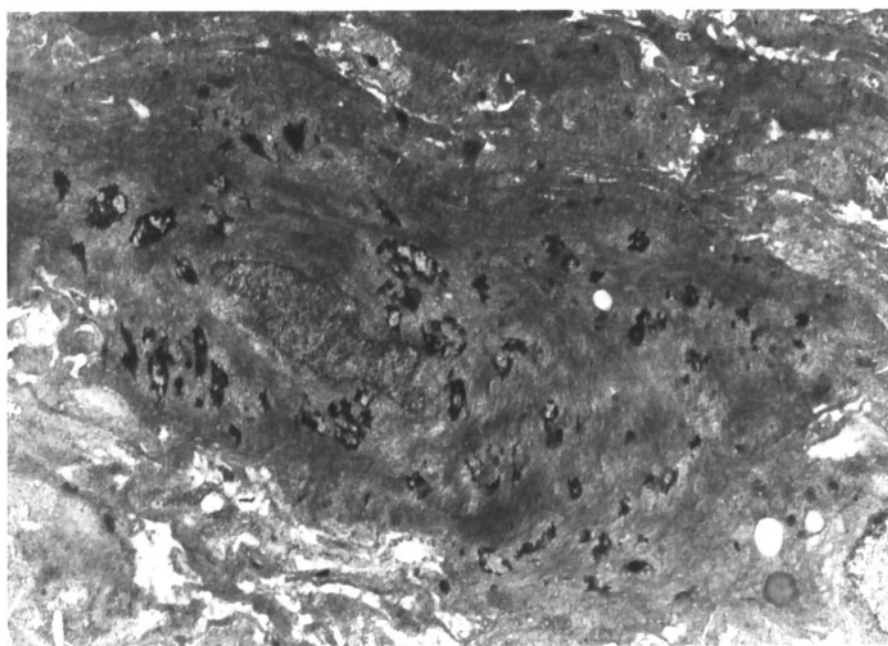


Fig. 5.15. Ependymoma, intracellular microfoci of calcification with a heterogeneous structure. Electron microscopy,  $\times 7000$

and other conditions. Importantly, hydroxyapatite crystals are found on X-ray spectrography [3001] (Fig. 5.14). Ca is found mainly as the phosphate form and the Ca to P ratio is identical on chemical analysis to that theoretically calculated for hydroxyapatite. Apart from Ca, numerous other minerals such as Fe, Na, Mg, Zn, Cu, and Pb are present, as shown by qualitative spectrography [2988]. In meningiomas, oligo-

dendroglomas, glioblastomas, and craniopharyngiomas, the elemental composition of the deposits seems to be characteristic of each type of tumor [775].

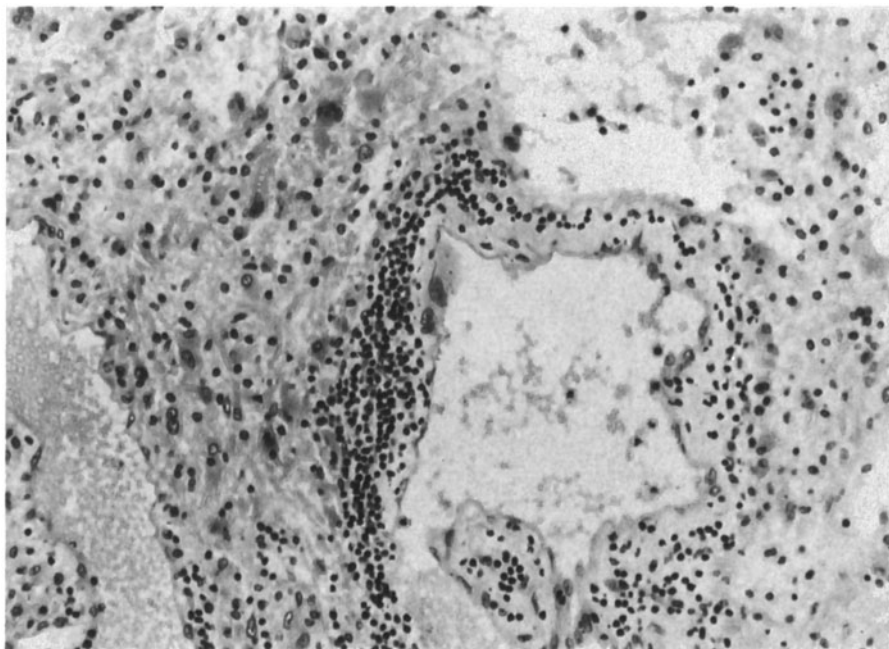
In all the calcifying conditions studied, it has been found that the organic matrix is "thirsty" for Ca, because of the presence of GAG [2988]. The hypothesis is that calcification occurs following the principles which regulate that in cartilage. In strongly calcified concretions within cerebral tumors, reactions for GAG are more evident after demineralization, and the intensity of the calcification is greater where acid radicals are of the sulfate type [2988], so that the interaction between acid radicals and Ca is supported. Whether Ca is bound also to the amino groups of proteins cannot be established, even after microspectrophotometric infrared studies. It is, however, certain that as the process progresses, the concretions lose the organic matrix, and their mineral component increases. In fact, after demineralization of old, heavily calcified concretions, the intensity of histochemical reactions of the matrix is much less than in more recent, less mineralized deposits. The enlargement of concretions is mainly due to hydroxyapatite crystals which show a strong surface activity and a high degree of ionic exchange *in vitro* [833], so as to be able to adsorb Ca or other minerals.

Electron microscopy has provided interesting information. In nontumor calcifying processes, it has been observed that deposits are found in the basement membranes of blood vessels or just outside them [1200, 2313, 2393]. They may appear as minute granules in the cytoplasm of adventitial cells and sometimes in glial processes, so that a suspicion has been raised that pericytes participate in this process [1727]. In tumors, the findings of heterogeneous microfoci of calcification is common and usually associated with a fibrous hypertrophy (Fig. 5.15).

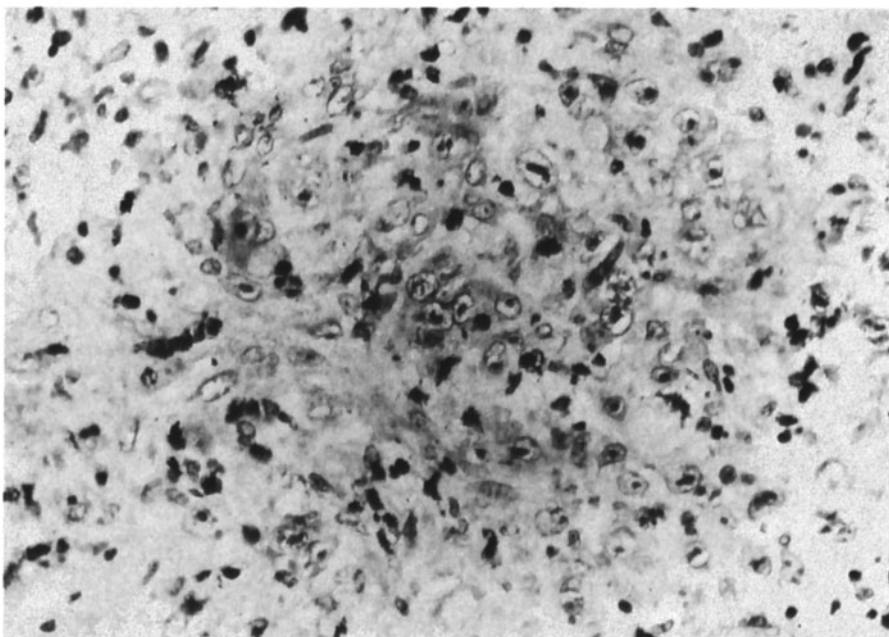
## 5.5 Immune Response

Undoubtedly, the nature and the efficacy of the tissue response to the tumor reflects the capacity of circulating lymphocytes to mount an immune response. In patients with gliomas, it has been noted that there is a degree of cellular and humoral anergy [350, 2242], which is in direct relationship to the degree of malignancy [2069, 352]. In particular, in those with malignant gliomas, the number of g-suppressor cells [1049] and of OKT8<sup>+</sup> lymphocyte subpopulations is high, whereas that of OKT4<sup>+</sup> is low [1466]. The low mitogenic index of circulating T lymphocytes [2853] and the increase of the T suppressors would cause a defect in the normal T lymphocyte response [3573].

Besides the finding of a defective cell-mediated immune system, signs of a local immune response consisting in the presence of mononuclear cell infiltrates are observed (Fig. 5.16a). Since the first description of lymphoid infiltrates in astrocytomas [223], mononuclear infiltration has been the object of numerous studies. In autopsy material, the lymphocytic reaction considered as an expression of the immune response is marked in 30% of gliomas, modest in 28%, and absent in 42% [2788]. In malignant gemistocytic astrocytomas, lymphocytic perivascular cuffings are particularly abundant [3379]. Furthermore, a correlation has been reported between survival and the amount of lymphocytic infiltration in malignant gliomas [2545, 351]. However, the opposite or no correlation has also been found [3008, 2914]. The peri-



a



b

**Fig. 5.16. a** Lymphocytic infiltrates in the vessel walls of a glioblastoma. H&E,  $\times 300$ . **b** Cerebral carcinomatous metastasis. Macrophages are evident by immunostaining for lysozyme. PAP-DAB,  $\times 400$



vascular infiltrate, predominantly lymphocytic with rare plasma cells, is more frequent in less malignant areas and lacking in necrotic and hemorrhagic areas. Parenchymal infiltration is present in 29% of gliomas, mostly in glioblastomas [351].

Attempts to characterize the mononuclear cell subpopulations in the infiltrates have yielded contrasting results. A prevalence of B lymphocytes has been noted by some, but other authors [3286, 3573, 2327, 2542] have stressed the presence and sometimes the predominance of T lymphocytes, in particular of the subpopulation OKT8<sup>+</sup> (suppressor/cytotoxic) [1340]. NK (natural killer) cells have also been isolated from malignant gliomas [2257] and are increased in number as compared with the peripheral blood [866]. It appears, therefore, that lymphocytes sensitized to glioma antigens escape from the circulation and gather in the tumor [3573], thanks also to the alteration of the BBB.

The type of local response revealed by the characterization of the subpopulations seems to indicate the presence of immunoregulatory factors. Lymphocytes infiltrating malignant gliomas have been isolated and cloned [2257]. The clones are capable in vitro of destroying allogenic and autologous cells to a greater extent than the peripheral blood lymphocytes in the same patients. However, their ability to clone is much lower than that of the circulating lymphocytes. It seems, therefore, that there is an accumulation of specific cytotoxic lymphocytes in the tumor, but their activity is limited by the presence of T cell-suppressive factors. A suppressive action has been attributed to anticonvulsants, anti-inflammatory drugs, specific immunoglobulins and circulating immune complexes [3208, 1036], and the close topographical relationships with tumor cells [2257]. Immunosuppressive factors have been found in glioma cyst fluid [1671] and in the serum of patients before operation [349]. A factor isolated from glioma cells in culture has been found to antagonize the effects of interleukins (IL)-1 and -2 [926]. It has been called "glioma-derived T cell suppressor factor," and it is able to suppress both the IL-2-dependent T cell proliferation and the generation of cytotoxic T cells in mixed lymphocyte cultures. It further suppresses lymphokine-activated killer (LAK) cell activity [1822] and is identical to transforming growth factor (TGF)- $\beta$ 2 [675, 282].

Other mechanisms have been proposed to explain the escape of gliomas from the immune response: a defect in immunogenicity and the secretion of a mucopolysaccharide coat. The interaction of glioma cells in culture with a macromolecular factor produced by peripheral blood mononuclear cells increases the production of this protective coat [725].

The role of macrophages in humoral immunity is clear, but little is known in relation to gliomas. They represent part of the infiltrating cells within primary and secondary tumors (Fig. 5.16b) with different percentage values in various studies, perhaps depending on the method used [3714, 2308, 850, 2850, 1340]. The entrance of macrophages into the tumor is essential to initiate the lymphocytic response and is due to the breakdown of the BBB. An alternative route is the transformation of microglia into macrophages, which may be triggered by the release of IL-3 from astrocytes, an event which has been documented in culture [960].

Macrophages in malignant gliomas are present in necrotic areas, in tumor parenchyma, and at the borders with normal tissue. They express class II major histocompatibility complex (MHC) antigens, a fact which led to the belief that they are involved in the immune response apart from phagocytosis [2850]. Glioma cells, reac-

tive astrocytes, and cerebral endothelial cells also express a human leukocyte antigen (HLA-DR). Its expression is potentiated by stimulation of  $\gamma$ -interferon [1050, 2641]. These cells are, therefore, able to present the antigen to lymphocytes [682].

In glioma patients, an autologous, humoral, nonspecific response against the tumor has been described. This response is not a direct one. In fact, even though B lymphocytes are present in gliomas, it is doubtful whether they produce glioma-specific antibodies which may participate in cytotoxic, cell-mediated complement-dependent or antibody-dependent reactions [2132, 79].

A modest antiglioma activity is present in the serum of patients, especially of those with low grade gliomas. This is probably related to an immunoglobulin G or M, but it is easily absorbed by platelets and other tumor cells [1755, 2132, 535].

## Classification and Nosography of Neuroepithelial Tumors

A century has now elapsed since the first attempts to classify cerebral neoplasms systematically. The identification of new cellular elements in the nervous tissue, their histogenetic classification, the discovery of other morphological tumor features and the accruing of biological data have progressively led to the classifications being updated. This has been facilitated by the progress in neurosurgery and, more recently, by the introduction of molecular biology into neuro-oncology.

It is opportune to discuss the actual status of the classification and nomenclature of cerebral tumors, to provide some historical data, and to follow, even if in broad terms, the conceptual development which allowed the classifications to be devised. To deal with neuroectodermal tumor classifications means to describe their history. However, it is difficult to resist the temptation to classify the classifications. Diverse criteria, i.e., morphological, histogenetic, biological, and organogenetic, and often more criteria at the same time, inspired earlier classifications.

Even though attempts to identify cerebral neoplasms had already been made, only with Virchow in 1863 [3555] was a systematic classification begun. The identification of the neuroglia by the German pathologist was followed by the description of “gliomas,” which he separated from the sarcomas and further subdivided into hard, soft, rich in cells, medullary, fibrotic, teleangectatic, and myxomatous. This parallelism between the description of particular cellular structures of the CNS and that of corresponding tumors was to last for several years. In fact, the description of “fibrillary cells” by Deiters [701] or “spider cells” by Jastrowitz [1514] was followed by the identification of the “spider cell gliomas” by Simon [3200]. The identification of blepharoplasts was followed by the description of ependymal tumors [2082], and so forth. The first classification inspired by unitary interpretative criteria was that of Pick and Bielschowsky in 1911[2636] who considered cerebral tumors as corresponding to the elements derived from the so-called undifferentiated neurogliocytes. These were considered to be multipotent elements from which neural, glial, and Schwann cells could arise. Along these lines, Ribbert [2776] perfected the systematics of cerebral tumors and thought of gliomas as being composed of glial cells. These tumors, in agreement with Cohnheim’s theory [548], could have originated from residues of tissues which remained isolated during embryogenesis and arrested at different developmental stages. Thus, the foundations for future and more complete histogenetic classifications were laid. In relation to developmental stages, tumors were arranged by Ribbert from the most immature to the more mature as follows: spongioneuroblastoma, spongioblastoma, glioblastoma, glioma, and neuroblastoma. Contemporary to Ribbert, a histogenetically based classification of tumors was published by Strauss and Globus [3324]. For these authors, the elements

of the cytogenesis of the neuroepithelium were in reciprocal relationship and were related to the tumors [1102].

It has to be remarked that these schemes, like other ones thus far followed, were oriented toward purely morphological classification criteria, i.e., they were based on the similarity the tumoral elements have with elements in cytogenesis. This system was nevertheless useful and susceptible to being encompassed in a more ample evaluation of cerebral neoplasia which, by taking into account the important data provided by clinical practice, could pretend to have an accomplished biological meaning.

Great progress was brought about by the development of neurosurgery and was made possible by the close cooperation between pathologists, neurologists, and neurosurgeons. This collaboration reached its peak in the association of Bailey and Cushing in 1926 [133]. Bailey correlated the various tumor cell types with the stages of maturation of the corresponding normal elements, as defined by histologists [1339, 416]. He first distinguished 15 tumor types, reduced in 1932 to ten, which could be matched to the medullary epithelium or its derivatives. These were medulloblastoma, neuroepithelioma, glioblastoma multiforme (to include the spongioblastoma multiforme [133, 1102] and the polymorphic glioma [2860]), pinealoma, spongioblastoma (which included the unipolar spongioblastoma [133] and the polar spongioblastoma [2601]), astroblastoma, astrocytoma, ganglioneuroma, ependymoma, and oligodendroglioma. This classification [133, 134], therefore, provided a histogenetic foundation for the various tumor types, as summarized in Fig. 6.1. With this classification, the authors also wanted to attribute a biological meaning to the diagnostic label, i.e., they wanted it to contain indications on survival, as inferred from clinical data, which were widely taken into consideration in the preparation of the definitive version.

According to survival criteria, Bailey [127] gave the following order of decreasing malignancy: medulloblastoma, neuroepithelioma, glioblastoma multiforme, pinealoma, ependymoma, astroblastoma, spongioblastoma, oligodendroglioma, ganglioneuroma, astrocytoma. Even if criticized and blamed for having stressed cytogenesis, which was not yet well understood, by creating even nonexistent elements such as the glioblast (to maintain in the system tumors such as the glioblastoma), this methodology of tumor classification represented, nonetheless, for the neurosurgeon and the neuropathologist an undoubted practical advantage, and therefore it was universally accepted.

Almost at the same time, another classification was developed by Roussy et al. [2860]. It was based on the similarity that tumor cells have with embryonal or mature elements and also took into account progressive or regressive events within the tumor. It comprised astrocytomas, fibrillary and nonfibrillary gliomas, glioblastomas, and spongioblastomas. Roussy, in fact, criticized the too exact identification of the tumor elements with the corresponding stages of maturation of the cells of the primitive epithelium used by Bailey, because he thought that the knowledge of the histogenesis of the CNS was still too fragmentary. In the atlas of Roussy and Oberling of 1931 [2861] it is stressed that the classification was based only on the similarity of the tumors with embryonal tissues. The following tumor types were named: (a) gliomas: astrocytoma, oligodendroglioma, glioblastoma; (b) ependymochoroidal tumors: ependymocytoma, ependymoblastoma, ependymoglioma, plexus-papilloma; (c) ganglioneuromas; (d) neurospongiomas; (e) neuroepitheliomas.

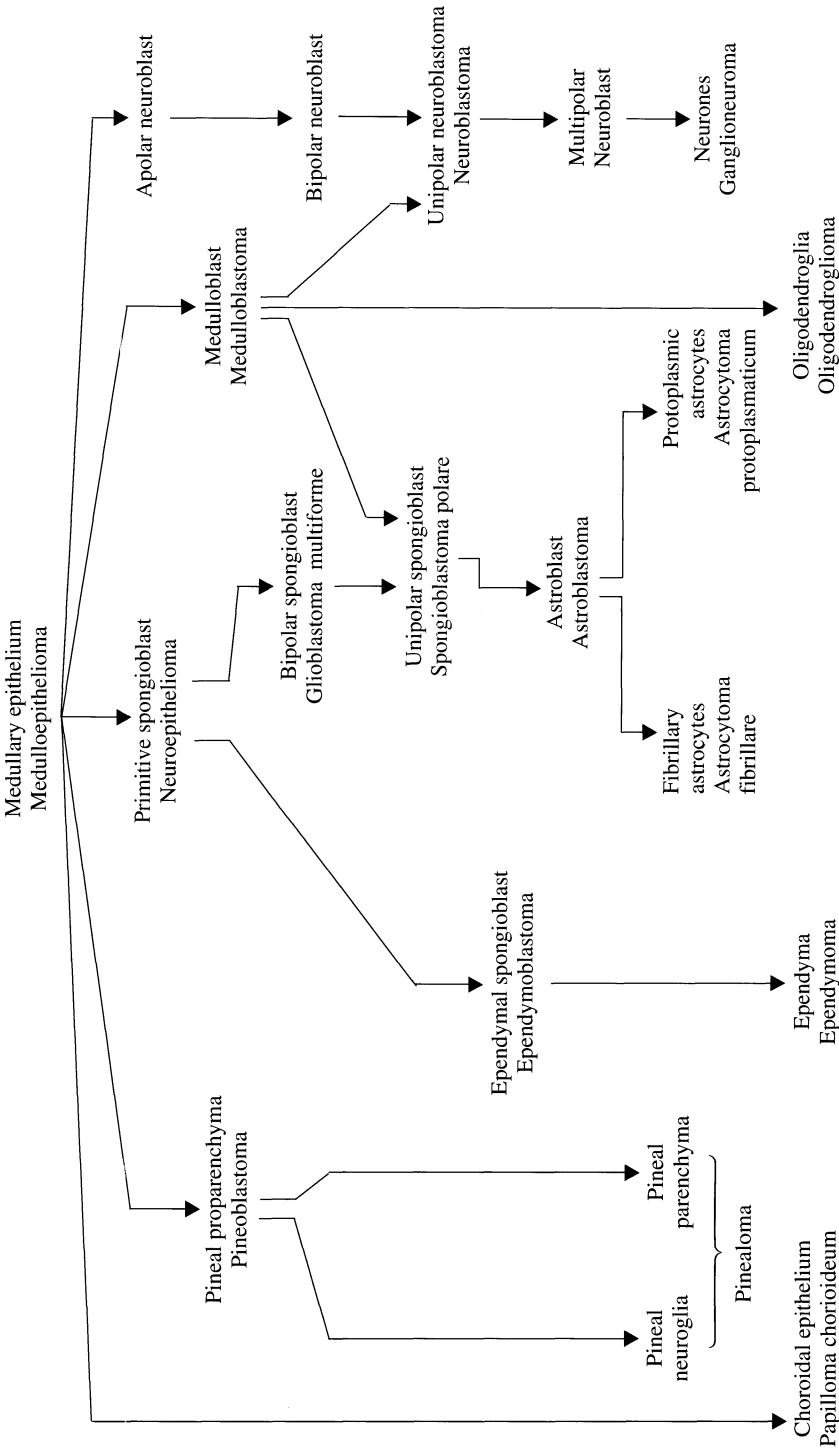


Fig. 6.1. Bailey's classification

Numerous other classifications were subsequently devised, including that of Penfield [2602], which was very close to that of Bailey and Cushing [133]. The names “piloid” astrocyte and “piloid” astrocytoma were introduced; the term piloid recalls the arrangement and the appearance of the isomorphous gliosis. The methodology of Bergstrand deserves special mention; he elaborated the surgical series of Olivecrona and accepted his subdivision into benign and malignant tumors [203, 204, 205]. Among the former, he included the fibrillary, the protoplasmic, and the gigantocellular astrocytoma and among the latter, the polymorphic, the fusiform, and the protoplasmic glioblastoma. The great merit of Bergstrand was, however, the separation of the cerebellar astrocytomas from the cerebral astrocytoma group; he called them “embryonal gliocytoma” and subsequently “glioneuroblastoma,” to underline their malformative character. This distinction found later not only morphological, but also valid biological foundations.

In the classification of Hortega [1393, 1394], the distinction was made between “gliomas” deriving from the glia proper and the “paragliomas” deriving from the ependyma, choroid plexus, pineal body, and so forth. This distinction was later to be accepted by Zülch [3799]. According to Hortega, cells which develop from the medullary epithelium can give rise on the one hand to gliomas, through the glioblast or “stem cells”, and on the other to paragliomas. The different glial types and, therefore, the different glial tumors, among which there could be transitional forms, would derive, in fact, from the glioblast. His classification was purely histogenetic and reflected the fact that he belonged to a school primarily interested in histology, particularly investigations with metal impregnation techniques. The tissue architecture was not sufficiently taken into account, and biological clinical data were almost lacking, so that there was a strong discrepancy between many tumor groups and their respective prognosis. Hortega’s classification is, accordingly, biologically based, difficult to interpret, and at variance with contemporary or immediately subsequent classifications. The diagnostic label given to a tumor after transferal into another biologically based classification system indicated a completely different tumor. For example, according to Hortega the term astroblastoma indicated a group of tumors with differing biological behavior. These tumors, therefore, were or will need to be placed individually under other names in classifications which had, or will have, taken biological data into account.

In the cerebral tumor system elaborated by Scherer [2982, 2984], the histogenetic classification had no meaning except for mature tumors, such as oligodendroglioma and astrocytoma. For other oncotypes, the cytological diagnosis was not useful to identify the elements of origin or to establish how these would have differentiated. Furthermore, the elements of the matrix were themselves tumor cells, i.e., modified cells. He underscored most of all the architecture of the tumor, the stroma, and tumor growth and distinguished, within the neoplasia proper, secondary and tertiary structures. Scherer’s system was more a principle than a true tumor classification, and the conclusions reached on prognosis were not fully consistent with clinical observations. The most important thing to be recalled is that, according to Scherer, there are no circumscribed astrocytomas; they all have a diffuse type of growth, and the majority undergo dedifferentiation toward glioblastoma. There would, therefore, be “primary” and “secondary” glioblastomas derived from astrocytomas, through a process which today is called anaplasia.

**Table 6.1.** Kernohan's classification

New	Old, with new in parentheses
Astrocytoma, grades 1–4	Astrocytoma (astrocytoma, grade 1) Astroblastoma (astrocytoma, grade 2)  Polar spongioblastoma (obsolete) Glioblastoma multiforme (astrocytoma, grades 3 and 4)
Ependymoma, grades 1–4	Ependymoma (ependymoma, grade 1) Ependymoblastoma (ependymoma, grades 2–4)  Neuroepithelioma (obsolete) Medulloepithelioma (ependymoma, grade 4)
Oligodendroglioma, grade 1–4	Oligodendroglioma (oligodendroglioma, grade 1)  Oligodendroblastoma (oligodendroglioma, grade 2–4)
Neuroastrocytoma, grades 1–4	Neurocytoma Ganglioneuroma  Gangliocytoma Ganglioglioma } (Neuroastrocytoma, grade 1)
Medulloblastoma	Neuroblastoma Spongioneuroblastoma  Glioneuroblastoma and others Medulloblastoma } (Neuroastrocytoma, grades 2–4)

Recognizing the great importance of anaplasia in the cytology of gliomas, Cox [586] proposed to classify them into tumors of adult tissue (astrocytoma, oligodendroglioma, ependymoma, pinealoma, and ganglioneuroma), anaplastic forms (glioblastoma multiforme), transitional tumors (astroblastoma, polar spongioblastoma), medulloblastoma, and rare tumors of the medullary epithelium and neuroepithelium. The classification of Chioventa [496], which was very complex because of the large numbers of subdivisions, belongs to this period. Chioventa recognized four groups of tumors: gliomas, neuromas (formed by neural cells), glioneuromas, and pinealomas. Gliomas were either typical or atypical. The former encompassed astrocytic, ependymal, and choroidal forms which could be mature or immature. The latter comprised glioblastomas belonging to diverse types. Various glial oncotypes were, therefore, distributed in this framework.

Extending the concept of anaplasia, limited to the glioblastoma by Roussy et al. [2860] and Cox [586], Kernohan et al. [1661] proposed a new classification of cerebral tumors, applying to them the principle of grading introduced by Broders [340, 341] for the epitheliomas and then extended by the Mayo Clinic to tumors in general. The different types of tumors did not develop from tissues at different stages of maturation but instead through a process of anaplasia which would come into play in

cerebral ontogenesis. For example, in their system of "grading" one passes through increasing degrees of anaplasia from the protoplasmic and fibrillary astrocytoma, through the astroblastoma, to the glioblastoma. In Table 6.1 this scheme is fully reproduced. This classification, by rejecting the histogenetic basis, is maximally simplified, also because some tumors, such as polar spongioblastoma and neuroepithelioma, are excluded. This classification offered several advantages at the practical neurosurgical level for which it was specifically designed. A new principle of systematization of cerebral tumors is thus introduced, borrowed from nonneurological pathology where it has led to good results, and applied to a tissue with a complex cell composition such as the nervous tissue.

The scheme of Kernohan et al. [1661] has been accused of not taking into account the regressive cellular changes which can produce a polymorphous picture, without changing the grade of malignancy. Diverse morphological aspects may be present in different areas, without the general biological behavior of the tumor being affected. If the "grading" is applied to a small biopsy fragment, the prognosis indicated by the diagnostic label may be wrong [3799]. The principle of "grading" could only be applied to autopsy material, when the entire neoplasm is examined, because anaplasia may be the result of a local phenomenon of lesser prognostic importance [2899]. The possibility that a tumor may be diagnosed as an astrocytoma on biopsy and as a glioblastoma at autopsy does not escape anybody's attention. On the contrary, in many glioblastomas it is not possible to find any sign uncovering their evolution from a more differentiated tumor. These tumors, therefore, must have had such a character since the onset (primitive glioblastomas of [2984]).

In many ways similar to the classification of Kernohan et al. [1661] is that designed with exclusively practical intent by Ringertz [2793]. Three grades, instead of four, are used (benign, intermediate, and glioblastoma) and applied to astrocytomas, ependymomas, and oligodendrogliomas. It is, however, to be stressed that the number of glioblastomas to be considered as originating from ependymomas and oligodendrogliomas is certainly less than could be deduced on the basis of their frequency. In this regard, it is important to highlight that anaplasia may proceed such as to erase any trace of the preceding tumor and, therefore, hamper the identification of the secondary origin of the glioblastoma. Even evaluating a glioblastoma as an anaplastic tumor originating from more differentiated tumors, the Swedish author is against abolishing such a term in the classification, as occurs in the scheme of Kernohan et al.

Another biomorphologic classification distinguished tumors deriving from parenchymal cells which form the CNS (oligodendroglia, astroglia, ependyma, and neural cells) from those deriving from cells of the adjacent organs (pineal cells and choroid epithelium) and from embryonal germs (neuroblastomas and medulloblastomas) [424].

In more recent years, the most accepted classifications have been those of Zülch [3799] and of Russell and Rubinstein [2899].

The classification of Zülch [2899] stems from that of Bailey and Cushing conceived not as an absolute dogma, but as a useful, working hypothesis. The tumors categorized by the American authors are maintained as biological entities, independent of their histogenetic problems. The intermediate aspects, the variations in type and so forth, are considered as variants which are specific for each group. Particular im-



portance is attributed to the regressive events as capable of modifying the morphology of a tumor; because of this they are considered as specific manifestations of the tumor. It has to be stressed that in this classification there are a certain number of nonclassifiable tumors. Adhering in part to the concept of Hortege, Zülch distinguishes neuroepithelial tumors into medulloblastomas, gliomas, paragliomas, and gangliocytomas. The medulloblastomas are undifferentiated tumors; the gliomas, paragliomas, and gangliocytomas are differentiated. Among the anaplastic tumors are the glioblastoma and, perhaps, the ependymoma and the anaplastic pinealoma.

The subdivision adopted by Russell and Rubinstein [2899, 2904] also appears to stem from that of Bailey and Cushing, with whom they share the concept of tumor types in which the cells recapitulate the stages of glial embryogenesis. This concept is, however, accepted only if the variations in shape and other cellular features are not indicative of an anaplastic process, which is notably frequent. Medulloblastoma is no longer a separate undifferentiated tumor but, instead, is encompassed within the tumors of the neuronal series because of the prevailing neuronal differentiation. In the classification of Zülch [3799], the medulloepithelioma does not exist as a tumor entity, and the majority of neoplasms containing neuroepithelial structures fall into the group of ependymomas, with which they share the same biological behavior. If medulloblastoma is considered as a tumor of the neuroblastic series [3324, 2899, 2904], there is a place for a medullo- or a neuroepithelioma which would be the true undifferentiated tumor originating from the "indifferent" cells of Schaper [2972]. In particular, the existence of the medulloepithelioma, reaffirmed by Globus and Cares [1100], has been emphasized by many authors [1517, 105, 2978, 2957] as the more primitive multipotential tumor of the CNS. The number of cases published is scanty; however, the importance of this oncotype in the relationship between tumors and cytogenesis is so high that it must be retained in the classification.

A second point of discrepancy between the two classifications is represented by the position of the polar spongioblastoma. While for Zülch [3799] it is a benign tumor arising from the subependymal glia and, therefore, always in relation with the ventricles and characteristically containing Rosenthal's fibers, for Russell and Rubinstein [2899, 2904] it is a rare and primitive malignant tumor. The problem is still a semantic one. With the term "spongioblastoma" Russell and Rubinstein refer to the spongioblasts of the cytogenesis. These are very immature elements, and therefore the corresponding tumor must have adequate characteristics of immaturity and malignancy. In effect, the tumor alluded to is malignant and immature, but it is extremely rare. Zülch, on the contrary, does not refer to the cytogenesis but to the resemblance of spongioblastoma cells to spongioblasts and employs the term to indicate a vast group of tumors, usually benign, including the so-called cerebellar astrocytoma, which in the nomenclature of Russell and Rubinstein are included among the pilocytic astrocytomas [3806]. The cerebellar spongioblastoma of Zülch is to be identified with all the types of cerebellar astrocytomas of Russell and Rubinstein. There are, however, no doubts about the biological behavior of this neoplasm. It is obvious that Rosenthal's fibers, thought by Zülch to be characteristic of spongioblastomas, are found by the other authors in astrocytomas.

Another point of controversy is the astroblastoma, not recognized by Zülch [3799] in the histogenetic sense [133] as a tumor entity, but as a feature which occurs in ma-

lignant gliomas and is therefore very close to glioblastoma. For Russell and Rubinstein [2899, 2904], on the contrary, it is a tumor *per se*.

The most important problem remains that of the glioblastoma. Zülch considers it a separate tumor, rarely originating from a preexisting astrocytoma [3406], in contrast with previous views [1661, 2793]. The possibility of anaplasia and the dedifferentiation of astrocytomas are satisfied with the creation of a group of malignant astrocytomas. By contrast, based on previous concepts [2984, 2793], Russell and Rubinstein discuss whether the category of glioblastoma should be maintained, as there is so much evidence for its origin following dedifferentiation of an astrocytoma; their anaplastic astrocytoma represents an astrocytoma in which the dedifferentiation may lead to glioblastoma.

Among the ependymal tumors, Russell and Rubinstein also accept subependymoma, arising from the subependymal layers and formed by a proliferation of subependymal astrocytes. The term subependymoma was coined by Scheinker [2973] to indicate already known and variously named tumors, which were subsequently renamed. The existence of such a tumor was denied by Zülch, according to whom it would be an ependymoma with pressure atrophy or a variant of spongioblastoma.

At the bottom of the debate on classification there are not only conceptual but also semantic problems. Certainly, both the creation of new names for tumors which were previously included under other labels and the keeping of old names for tumors which instead have acquired a new position have contributed to the polymorphism of the nomenclature.

A symposium on the classification of cerebral tumors was held in Cologne in 1962 with a long discussion on nomenclature. A scheme elaborated in 1958 by the Union Internationalis Contra Cancrum (UICC) as a basis for discussion was presented [1233]. In this symposium, the three main classifications were confronted, i.e., Kernohan et al., Zülch, and Russell and Rubinstein. The “grading” scheme according to Kernohan et al. was defended [2965]. Since the principles of Cohnheim [548] and Ribbert [2776] underlying the recent histogenetic classifications are no longer tenable, it is likely that tumors arise because of some disturbance of the adult cell. Several examples of tumors produced by external agents support this concept. The “grading” system is based, in fact, on the deviation of cells from the normal cytotypes, i.e., on the degree of dedifferentiation present and not on the possibility that, in the development of the tumor, the cells gradually become more malignant, as is erroneously thought. The grade with which a tumor is labeled depends on the time when cells are struck by the cancerous deviation. The naming according to grades does not imply a clinical judgment but refers only to cell metabolism, and the use of four grades is not qualitatively different from that of three grades, widely applied by everyone, when the terms semibenign, semimalignant, and intermediate are introduced. Finally, the criticism that the “grading” system provides a diagnosis-prognosis derived from very small tumor fragments while considering the inhomogeneity of several brain tumors was applied by Sayre to any examination of this type, independently of the classification scheme followed.

In 1979 the World Health Organization (WHO) published a classification based on the work of various groups [3802] which provided a compromise between that of Zülch and that of Russell and Rubinstein. The position of each oncotype in relation to the degree of malignancy was also indicated. This new classification was not unan-

imously accepted and several criticisms were made, especially in the new systematization of the degrees of malignancy. Glioblastoma, for example, was kept separate from astrocytic tumors and put into the group of poorly differentiated and embryonal tumors. Astroblastoma was maintained as a variant of astrocytoma, in spite of its recognition as a separate entity [1439, 1352].

In the years which followed, a remarkable amount of data has been produced in the different fields of neuro-oncology: immunohistochemical demonstration of new antigenic expression in tumors with their relationship to cytogenesis, molecular biology revelations with their putative relationship to pathogenesis, identification of new tumor subgroups on the ground of statistical studies of survival (on which topic many contributions accumulated [1073, 3698, 2402, 544, 995, 2329, 3026, 3032]) and identification of new tumor entities. As examples, the problem of primitive neuroectodermal tumors (PNET) [2829, 183], pineal tumors [1254], polar spongioblastoma, and many others regarding meningiomas [1643] required a new consensus on classification.

The problem of PNET can be regarded as paradigmatic. The term was first introduced by Hart and Earle in 1973 [1249] to label 23 tumors which could not be classified into any of the known categories and were characterized by undifferentiation, malignancy, circumscription, cyst formation, and appearance in young subjects. In the past decade, studies [184, 2827, 2830] again suggested grouping together tumors composed of undifferentiated neuroectodermal cells, with or without foci of differentiation, occurring in the CNS of children or young adults in different locations.

All further descriptions [2561, 284, 1761, 778, 1006] indicated one or more differentiations. Rorke [2827] proposed a scheme based on the concept that these tumors, first of all medulloblastoma, derived from the neoplastic transformation of primitive neuroepithelial cells, undifferentiated but capable of differentiating along neuronal, glial and ependymal lines. Subsequently, a modification of the WHO classification was proposed in order to include the group of PNET which was composed of medulloblastoma, neuroblastoma, pinealoblastoma, and ependymoblastoma [2830].

The most important question is whether or not the use of the term PNET is a simplified and more reliable tool to categorize embryonal tumors. Undoubtedly, it is an attempt to define tumors not easily classifiable, because of their uncertain nature by means of descriptive instruments instead of referring to the "cells of origin" [2829]. However, if only undifferentiated tumors are considered, the problem is practically restricted to medulloblastoma. Becker and Hinton [184] found 112 medulloblastomas in a series of 127 undifferentiated tumors. In our series, 112 out of 117 were found [3028]. In order to avoid confusion, since the term medulloblastoma is used too much by clinicians, it has been proposed to limit the term PNET to supratentorial tumors [3447].

The next question is whether medulloblastoma is a tumor specific to the cerebellum or a primitive undifferentiated tumor, together with similar supratentorial tumors of the pineal region and of the spinal cord, independently of the nature, uniformity, or multiplicity of the primitive undifferentiated cells [2830].

Several objections have been made to the PNET categorization. First, since the undifferentiated nature of the cells is emphasized, the system might accept cells that are simply unidentifiable and thus become a category of undiagnosed tumors; second, it includes heterogeneous and noncomparable tumors; and, third, it does not take ana-

plasia into due consideration [2873]. As anaplasia is a progressive phenomenon, it could be responsible for the undifferentiated appearance of a tumor. Medulloblastoma could, for example, be the anaplastic end stage of an astrocytoma [2352, 2885, 3059]. Not only is it difficult to distinguish between embryonic and anaplastic tumors, but the maturation of an undifferentiated tumor could also go unrecognized [156, 878, 1303]. Application of the PNET system might largely depend on the interpretation of the cell forms, and thus it might be impossible to obtain uniform diagnoses from different examiners. A better knowledge of the embryological origin is required; reliable prognostic evaluations cannot be made on the basis of the histological results as a similar morphology does not imply a similar biology [2214].

A panel of well-defined and extensively characterized Mabs was used on a series of pediatric brain tumors: In one third, both neuronal and glial differentiation was present [2295], as were positive neuroendocrine markers [1145]. These observations support the PNET concept, even though 35 out of the 37 cases studied were located in the posterior fossa, i.e., they were medulloblastomas. However, it has been proposed that, in order to distinguish primitive cells showing differentiation from undifferentiated primitive cells, the former should be called "neuroectodermal cells" committed to neuronal, astrocytic, or ependymal differentiation. Molecular biology data reported deletions on 17q or 17p or *myc* amplification [231, 2709]; the neural and neuroendocrine protein gene product 9.5 isolated from human brain [1485] has been demonstrated in 21 tumors [1244] even though they were obtained from posterior fossa tumors, i.e., medulloblastomas. Still other immunohistochemical findings are available concurring to define characteristics of PNET. In some cases different cytokeratin proteins, together with S-100 protein and vimentin, were expressed, indicating a wide range of differentiation patterns in PNET of early infancy [1172]. Other investigations showed that whereas astrocytomas and ependymomas are positive for nerve growth factor receptor (NGFR), only few PNET are positive, these being the ones with astroglial differentiation [137]. A systematic immunohistochemical study of ontogenesis and of PNET demonstrated that in these tumors a certain recapitulation of the ontogenetic development of differentiation is present [1706].

PNET have been indirectly associated with cerebellar dysplasias in humans. The dysplasias appear in fetuses as cell clusters resembling primitive neuroepithelial cells or cells of the cerebellar external granular layer. Later, they become more complex, even showing ganglion cells. They possess mitotically active cells and hypothetically may be the target of neoplastic transformation into PNET or other tumors [3738].

The use of the term PNET has practical and theoretical meanings. From the practical point of view, it indicates tumors with various kinds of differentiation and with a variable amount of cells which appear undifferentiated [2829]. From the theoretical point of view, the problem of the existence of a common, primitive, undifferentiated tumor cell (or cells) is of paramount importance, even though the meaning of the term "primitive" has not been further specified [183, 2829]. The concept of PNET is based on a criticism of the cytogenetic scheme of embryonal neuroepithelial tumors, because of the impossibility of predicting the differentiating potential or of establishing the ancestry of primitive neuroepithelial cells in a tumor by current morphologic techniques [1142, 2829]. It is also based on the observation that tumors are composed of primitive neuroepithelial cells whose differentiation does not necessarily follow normal schemes [2829].

Perhaps a definitive system of classification, taking into account all these points of view, is not possible. Classifying cerebral tumors also means making a histological diagnosis and recognizing histological prognostic factors. There are a number of limiting factors, one of which is the reproducibility of the histological diagnosis. Within the confines of the Childhood Brain Tumor Consortium (CBTC), for example, the reproducibility of the systematization in the diagnostic classes of the WHO has been evaluated. The Px, or conditional probability of agreement between different neuropathologists, has been found to vary for various tumors. The pilocytic astrocytoma, ependymoma, medulloblastoma, and astrocytoma have lower values, and the use of a single category of "astrocytoma" to include the fibrillary and protoplasmic varieties is recommended. It is also suggested that the criteria of anaplasia in astrocytomas and ependymomas be redefined [492]. Another point of great difficulty is to establish a grading system which could also take into account clinical and therapeutic parameters while satisfying at the same time the clinical necessities [663, 652, 387]. Advances in antigenic expression analysis and molecular biology oblige us to leave the matter of classification open. However, for the present, after meetings held in Houston (1988) and Zürich (1990), a new version of the WHO classification has been presented [1702]. In principle, its suggestions are followed in the present book.

For the classification scheme the reader must refer to the booklet of Kleihues et al. [1702] and to the many presentations of the main problems [1702a, 3517]. For nosographic problems concerning individual tumor types, see the relevant chapters.

## Classification of brain tumors by WHO 1993 [1702]

***Tumours of Neuroepithelial Tissue****Astrocytic tumours*

## Astrocytoma

Variants: Fibrillary

Protoplasmic

Gemistocytic

Anaplastic (malignant) astrocytoma

## Glioblastoma

Variants: Giant cell glioblastoma

Gliosarcoma

Pilocytic astrocytoma

Pleomorphic xanthoastrocytoma

Subependymal giant cell astrocytoma

(Tuberous sclerosis)

*Oligodendroglial tumours*

## Oligodendroglioma

Anaplastic (malignant)

oligodendroglioma

*Ependymal tumours*

## Ependymoma

Variants: Cellular

Papillary

Clear cell

Anaplastic (malignant) ependymoma

Myxopapillary ependymoma

Subependymoma

*Mixed gliomas*

Oligo-astrocytoma

Anaplastic (malignant)

oligo-astrocytoma

Others

*Choroid plexus tumours*

Choroid plexus papilloma

Choroid plexus carcinoma

*Neuroepithelial tumours**of uncertain origin*

Astroblastoma

Polar spongioblastoma

Gliomatosis cerebri

*Neuronal and mixed neuronal-glial tumours*

Gangliocytoma

Dysplastic gangliocytoma

of cerebellum (Lhermitte-Duclos)

Desmoplastic infantile

ganglioglioma

Dysembryoplastic neuroepithelial tumour

Ganglioglioma

Anaplastic (malignant)

ganglioglioma

Central neurocytoma

Paranglioma

of the filum terminale

Olfactory neuroblastoma

(Aesthesioneuroblastoma)

Variant: Olfactory neuroepithelioma

*Pineal parenchymal tumours*

Pineocytoma

Pineoblastoma

Mixed/transitional pineal tumours

*Embryonal tumours*

Medulloepithelioma

Neuroblastoma

Variant: Ganglioneuroblastoma

Ependymoblastoma

Primitive neuroectodermal

tumours (PNETs)

Medulloblastoma

Variants: Desmoplastic

medulloblastoma

Medullomyoblastoma

Melanotic medulloblastoma

***Tumours of Cranial and Spinal Nerves****Schwannoma*

(Neurilemmoma, Neurinoma)

Variants: Cellular

Plexiform

Melanotic

*Neurofibroma*

Circumscribed (solitary)

Plexiform

*Malignant peripheral nerve sheath tumour (MPNST) (Neurogenic sarcoma, Anaplastic neurofibroma, "Malignant schwannoma")*

Variants: Epithelioid

MPNST with divergent

mesenchymal and/or

epithelial differentiation

Melanotic

## Classification of brain tumors by WHO 1993 [1702]

***Tumours of the Meninges****Tumours of meningotheial cells*

## Meningioma

## Variants: Meningothelial

Fibrous (fibroblastic)

Transitional (mixed)

Psammomatous

Angiomatous

Microcystic

Secretory

Clear cell

Chordoid

Lymphoplasmacyte-rich

Metaplastic

## Atypical meningioma

## Papillary meningioma

## Anaplastic (malignant) meningioma

*Mesenchymal, non-meningothelial tumours**Benign neoplasms*

## Osteocartilaginous tumours

## Lipoma

## Fibrous histiocytoma

## Others

*Malignant neoplasms*

## Hemangiopericytoma

## Chondrosarcoma

## Variant: Mesenchymal chondrosarcoma

## Malignant fibrous histiocytoma

## Rhabdomyosarcoma

## Meningeal sarcomatosis

## Others

*Primary melanocytic lesions*

## Diffuse melanosis

## Melanocytoma

## Malignant melanoma

Variant: Meningeal  
melanomatosis*Tumours of uncertain histogenesis*

## Haemangioblastoma

## (Capillary haemangioblastoma)

***Lymphomas and Haemopoietic Neoplasms***

## Malignant lymphomas

## Plasmacytoma

## Granulocytic sarcoma

## Others

***Germ Cell Tumours***

## Germinoma

## Embryonal carcinoma

## Yolk sac tumour

## (Endodermal sinus tumour)

## Choriocarcinoma

## Teratoma

## Immature

## Mature

## Teratoma with malignant

## transformation

## Mixed germ cell tumours

***Cysts and Tumour-like Lesions***

## Rathke cleft cyst

## Epidermoid cyst

## Dermoid cyst

## Colloid cyst of the third ventricle

## Enterogenous cyst

## Neuroglial cyst

## Granular cell tumour

## (Choristoma, Pituicytoma)

## Hypothalamic neuronal

## hamartoma

## Nasal glial heterotopia

## Plasma cell granuloma

***Tumours of the Sellar Region***

## Pituitary adenoma

## Pituitary carcinoma

## Craniopharyngioma

## Variants: Adamantinomatous

## Papillary

***Local Extensions  
from Regional Tumours***

## Paraganglioma (Chemodectoma)

## Chordoma

## Chondroma

## Chondrosarcoma

## Carcinoma

***Metastatic Tumours******Unclassified Tumours***

## The Concept of Malignancy: Anaplasia, Cell Proliferation, Metastasis

### 7.1

#### General Considerations

In intracranial tumors the concept of malignancy has a clinical and a biological sense. Contrary to tumors in other organs, intracranial tumors grow within a closed space whose only reserve depends upon shifts in the cerebrospinal fluid (CSF). The brain and the spinal cord are formed by different structures composed of cells in various stages of differentiation: They are, therefore, inhomogeneous from an anatomical and functional point of view. While some cerebral structures may withstand severe damage for a long time without the life of the patient being compromised, others cannot tolerate, even for a short time, minimal damage. A tumor, therefore, may be “malignant” and lead to a fatal outcome solely on the basis of its location. Given the same histological appearance, an astrocytoma of the aqueduct will be more “malignant” than a similar astrocytoma in the hemisphere. The criteria of operability also play a role, so that an astrocytoma of the third ventricle may be more “malignant” than an analogous tumor of the cerebellar hemisphere.

The concept of biological malignancy refers instead to the proliferating potential of the neoplastic cells which conditions the histological and other features of the tumor, rapid infiltrative and destructive growth, recurrence after surgical removal, and metastasis as for tumors in other organs. The histological signs of malignancy depend on the genuine growth potential of the tumor.

The cellular appearances of neuroepithelial tumors in some way correspond to those shown by the normal stages of neurocytogenesis up to the final differentiation step. Concepts such as dedifferentiation, anaplasia, and cellular atypia were often expressed in the older literature. Atypia was meant to express the taking on by tumor cells of morphological and metabolic properties no longer reconcilable with the stages of cytogenesis, either of the same series to which tumor cells belong or of other series. The concept of anaplasia was related instead to dedifferentiation, which meant the loss of morphological molecular characteristics typical of that grade of differentiation and a return to the characteristics of earlier stages. Alternatively [3786] anaplasia meant simply the process by which cells failed to differentiate, never reaching morphological maturation. In practice, atypia should follow anaplasia.

Many of the morphological structural features of glial tumors, such as the malignant transformation of astrocytomas, may be described dynamically along the lines of cellular dedifferentiation. The foundations of the different “grading” systems [1661, 2793] are still valid if cell dedifferentiation is considered in relation to the neoplasm as a whole.



The histological signs indicative of malignancy are nuclear polymorphism, immature appearance of the cells, absence of one or more features of differentiation, alteration of the nucleocytoplasmic and nucleolo-nuclear ratios, nuclear hyperchromasia, formation of giant or polynucleated cells, presence of mitoses (especially if atypical), regressive events such as necrosis and stromal changes. None of these characters may be considered by itself as indicative of malignancy, since any of them may be found in nonmalignant tumor conditions or even in pathological nontumor conditions as a secondary nature.

The divergence of opinions regarding the DNA content of neoplastic cells and the meaning of nuclear hyperchromatism, which were much debated topics in the past, no longer exists, even though the ploidy and the frequency of mitoses remain important diagnostic characteristics. The morphology of a tumor represents the result of a series of hierarchical biological events. The prognostic value of a malignant histological phenotype must be confirmed by a statistical analysis of survival.

In human pathology, there are no systematic observations on the early stages of development of brain tumors, only reports of neoplasms occasionally found at autopsy [1448]. However, by considering the frequency of the different oncotypes in adults and children, and their mode of growth, and by comparing them to known experimental models, especially those obtainable with nitrosourea derivatives, general trends may be identified.

Fetal neuroepithelial cells in the latest stages of development may be the target of neoplastic transformation [2886, 2873], as are neuroepithelial cells of the five additional loci where neurocytogenesis also occurs in postnatal life [1944], i.e., the subependymal zone, the astrocytes and oligodendrocytes during myelinogenesis, the external granular layer of the cerebellum, the fascia dentata of the hippocampus, and the molecular subpial layer of the cerebral cortex.

Neoplastic transformation may occur in successive steps as the target cells differentiate and migrate. As a consequence of this displacement, the tumor may "arise" at sites away from that of the first transforming event [2886]. The essential factor is that the target cell must still be capable of multiplying at the time the transforming event occurs [2886]. The "neoplastic vulnerability" of neuroepithelial cells varies according to a series of factors: the existence of a reserve population of stem cells, the ability of already differentiated cells to reenter the cell cycle, the number of cells in cycle at risk at a given time, the time period during which a given cell population remains in the cycle and its state of differentiation [2876]. Taking into account that the neuroepithelial cells struck by the neoplastic transformation continue to differentiate, and that differentiated tumors may undergo anaplasia, the formal pathogenesis of gliomas must be discussed in terms of the bipolarity differentiation/dedifferentiation.

Astrocytomas can be considered an example of differentiation after transformation. An interesting observation has been made on this. The majority of astrocytoma cells are glial fibrillary acidic protein (GFAP) positive but negative for A2B5 and galactocerebroside (GC) antibodies. This combination would indicate an origin from type 1 astrocytes. Few tumors, and only those of low grade malignancy, contain A2B5- and GC-positive cells [259]. Once malignancy arises, the already mentioned typical histological signs appear.

Contrary to what occurs in other organs, the number of CNS cells susceptible to neoplastic transformation in adult life is minimal, and these cells usually have a low

turnover. Therefore, even though a tumor may arise from the neoplastic transformation of neuroepithelial cells in adult life, most tumors derive from the transformation of neuroepithelial cells during embryonal morphogenesis. One must also consider that the differentiation of transformed neuroepithelial cells does not necessarily follow normal schemes: Specific characteristics of a certain normal cell type may be expressed by transformed cells following alternative avenues of differentiation. An example may be the expression of GFAP in the plexus papilloma [2876] or the development of striated muscle fibers in medulloblastoma; thus, differentiation could be metaplastic or heteroplastic.

The more precocious the cytogenetic stage at which transformation occurs, the more numerous the lines of differentiation which the tumor may express. A typical example of this is medulloepithelioma [2978, 2957]. On the other hand, the shorter the susceptible cytogenetic phase or the lower the susceptibility to transformation, the rarer the related tumor. An example of this is also the very rare medulloepithelioma, which represents the neoplastic counterpart of the earliest and shortest development stage. Cerebral neuroblastoma could correspond to a longer late stage, but it is also rare because when neuroblasts migrate they no longer replicate, and thus the tumor can differentiate in only one direction. The greater frequency of peripheral neuroblastoma would be due to the longer period of migration and proliferation of the cells of the sympathetic system. Desmoplastic ganglioglioma has been given as an example of a rare tumor, because the vulnerability of its corresponding embryonal elements is limited in time [2876]. Tumors like medulloblastoma and gliomas in general, whose corresponding embryonal cell counterparts have a long period of vulnerability, are more frequent. The precursor cells of medulloblastoma remain a long time in a mitotically active phase and are located primarily in the external granular layer of the cerebellum. For gliomas, the long period of vulnerability is due to the persistency of glial cell turnover during adult life.

The main difficulty, especially with gliomas, is represented by the relationship between benign and malignant forms. Glioblastoma is considered the end result of progressive anaplasia in astrocytoma. The cells go from the nonproliferative to the proliferative pool, the growth fraction increases, and signs of increased proliferation, such as a high number of mitoses and high cell density appear. Angiogenesis and necrosis take place, with all the known histological consequences.

The neoplastic transformation is a multistep process which occurs in stages. Morphologically, through anaplasia, tumor progression proceeds to the final malignant features of the neoplasm as commonly seen on biopsies and at autopsy. It may be defined as a series of consecutive alterations of multiple units: growth rate, invasive capacity, ability to grow freely in body fluids and independently of hormones [937]. Subclones replace the predecessors. The pathology may be interpreted as the result of a dynamic continuum in which the most important characteristic is selection by competition [3058, 1704].

The growing amount of data arising from molecular studies enables the tentative description of the processes of neoplastic transformation and progression of gliomas in terms of genetic events underlying the phenotypic changes. Starting from the observation that, at least partially, the molecular events described in Chap. 2 of this book are selectively detectable in the various types and degrees of malignancy of gliomas, different pathways of glioma development have been proposed [552, 3568, 516, 2013, 3616a].

The formation of astrocytomas seems to be associated with the inactivation of the p53 tumor suppressor gene, the allelic loss of chromosome 22q at a locus other than NF2 gene, and growth stimulation by an autocrine loop mediated by platelet-derived growth factor (PDGF) and its receptors, particularly the  $\alpha$ -receptor. These three molecular events may be observed in well-differentiated astrocytomas, as well as in the anaplastic ones, and in glioblastomas, obviously suggesting a role in early phases of astrocytoma development.

The passage to anaplastic astrocytoma is marked by allelic losses of chromosomes 9p, 13q, and 19q, which can be frequently found in anaplastic astrocytomas and in glioblastomas, but are uncommon in astrocytomas. In at least some malignant gliomas, allelic loss on 13q is related to RB1 tumor suppressor gene, whereas the tumor suppressor genes on 9p and 19q associated with gliomas are not known. The appearance of epithelial growth factor receptor (EGFR) gene amplification and of allelic losses on chromosome 10 marks the transition from anaplastic astrocytoma to glioblastomas. Loss of heterozygosity (LOH) on 10p and 10q are more frequent in glioblastomas than EGFR gene amplification, but EGFR gene amplification is virtually always associated with allelic loss on chromosome 10 and almost never associated with p53 mutations and LOH on 17p. These observations are in agreement with two distinct pathways leading to glioblastomas. The first one includes p53 gene mutations and other events described in astrocytomas and anaplastic astrocytomas; it occurs in relatively younger patients and would lead to the development of secondary glioblastomas through loss of chromosome 10 loci. The second one, characterized only by the association of EGFR gene amplification with 10p and 10q loss, occurs in older patients and would correspond to the development of "primary" glioblastomas. Following this scheme, a glioblastoma could also arise from an oligodendroglioma or from an oligoastrocytoma by chromosome 10 loss. The hallmark of this alternative pathway would be the presence of the association of 19q and 1p losses, which are characteristics of oligodendroglial tumors of all degrees of malignancy.

The description of the pathways of neoplastic progression in gliomas is largely incomplete and will probably be revised with the progress of knowledge on molecular mechanisms involved. In particular, the occurrence of the various events is not completely exclusive to the distinct oncotypes, but the description is based on their preferential distribution in gliomas. However, this appears a promising and more precise approach to the description of biological heterogeneity characterizing malignant gliomas.

Anaplasia is now interpreted as the result of genotypic heterogeneity, a consequence of the genetic instability of tumor populations and of the progressive increase of the mutation rate, conditioning a phenotypic heterogeneity. Anaplasia may also be considered either as a maturation arrest [3786] or as an accelerated growth of already differentiating cells [411]. This concept interlocks with that of "stem cells" whose existence has been postulated but as yet not demonstrated. They do not need to be the same as those of cytotogenesis. Independently of their identification with "primitive, undifferentiated" cells and of their capability to express differentiation antigens, which is a crucial point in neuro-oncology, it is sufficient that they can re-enter the proliferative cycle, as seems possible for astrocytes and oligodendrocytes [2037]. On the morphological level, cellular atypia, which is not necessarily present, is the first consequence of anaplasia.

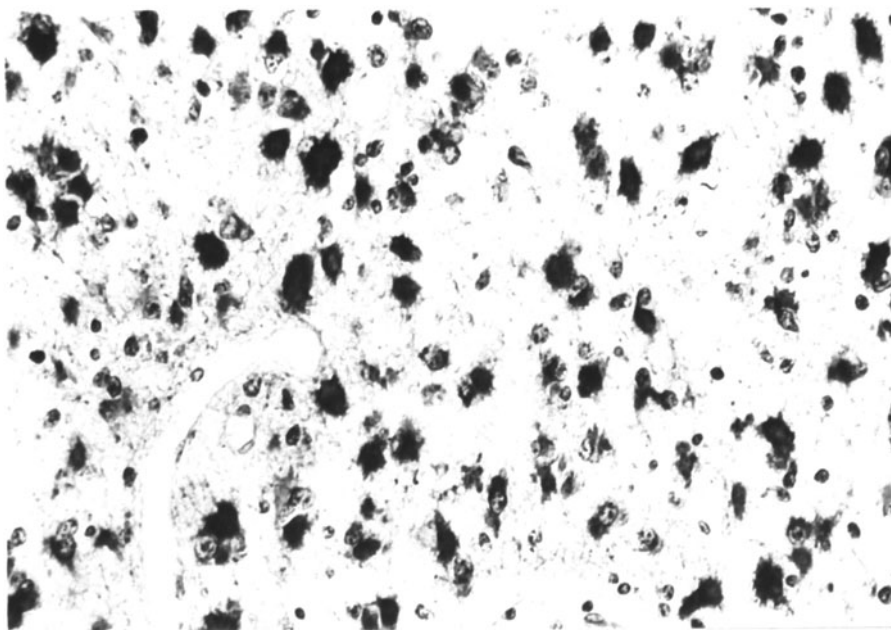


Fig. 7.1. Astrocytoma. All cells express glial fibrillary acidic protein (GFAP). (From [2994]). PAP-DAB,  $\times 400$

Cell heterogeneity has been documented by karyotypic analysis, [2112, 3138], cytophotometry, flow cytometry [1401], and comparison between established cell lines [244]. It remains to be established whether all the phenotypic variations are also genetic, and how or whether they depend on epigenetic factors [242, 2886].

With the occurrence of anaplasia, the growth fraction increases [1400] because cells are transferred to the proliferative pool leading to a series of phenomena characterized by an increase in cell density, and proliferative activity. These events are a direct consequence of the increase of the growth fraction, while other, maybe overestimated features at the histological level such as nuclear polymorphism, cellular monstrosity, and in part also necrosis are indirect consequences.

The increase in number of mitoses and cell density may, however, be a phenomenon circumscribed within the tumor, at times easily missed in the histological examination, so that beginning anaplasia may go unrecognized.

An example of anaplasia by cell heterogeneity is given by expression of GFAP, the characteristic marker of astrocytic differentiation [667, 298], evaluated as an element of heterogeneity [1552]. In gliomas, it is found in all cells with fibrillogenic capacity, and its expression is inversely correlated with the degree of anaplasia [828, 3507, 3533]. GFAP is lacking in too primitive and in anaplastic cells. It has to be emphasized that the small hyperchromatic cells, which proliferate rapidly [1400] and are responsible for tumor invasion and growth in glioblastoma [1065], are GFAP negative [3533]. The appearance of anaplasia in astrocytoma and the active cell proliferation in glioblastoma are sustained by the progressive increase of a cell population rich in mitoses, with isomorphous nuclei and negative for GFAP [3024, 1821] (Figs. 7.1–7.3).

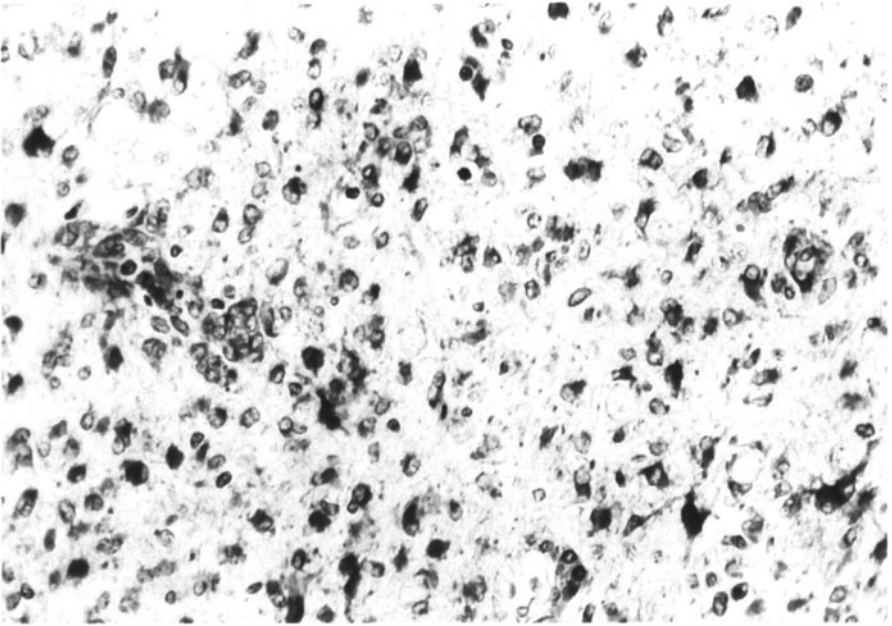


Fig. 7.2. Anaplastic astrocytoma. Some cells still express glial fibrillary acidic protein (GFAP), but many are negative and mitoses are present. (From [3024]). PAP-DAB,  $\times 400$

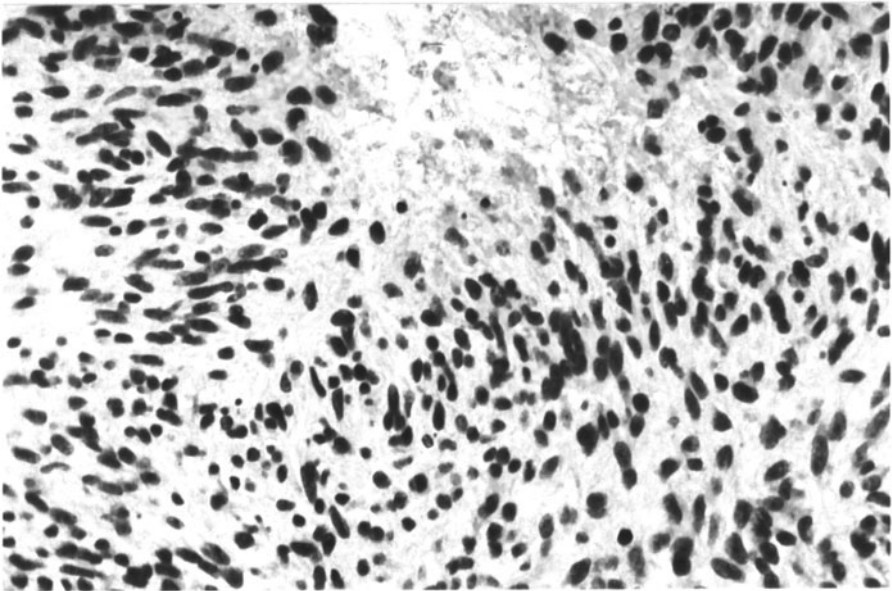


Fig. 7.3. Glioblastoma. In the proliferating area, no cells express glial fibrillary acidic protein (GFAP). PAP-DAB,  $\times 400$

The recognition of the malignant transformation *in vivo* is of paramount importance. It is a matter of everyday debate, especially after the introduction of new imaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI), and stereotactic biopsies. Practically speaking, the most common problem encountered in histological diagnosis concerns the degree of malignancy. It could be related to a surgical sampling error, for example, in small specimens taken by stereotaxis. In this regard, the importance of imaging in the interpretation of the histological findings must be stressed. It is also possible that malignant transformation can occur after the histological diagnosis has been made. Since anaplasia may be a localized and mild rather than a generalized and intense phenomenon [2903], it may be missed both histologically and by neuroimaging; it may be detected only when it reaches a certain extension and intensity.

## 7.2 Cell Kinetics

Growth fraction, number of mitoses, nuclear polymorphism, and nuclear hyperchromatism are all indicators of the proliferative capacity of a tumor.

It is not exactly known when and how cell proliferation is triggered in tumor progression. Generally, any qualitative or quantitative change in the codified proteins involved in the signal transduction may be instrumental in cell proliferation. In the ras family, the stabilization of the protein in the active state may lead to a continuous flow of signal transduction. Transcription factors, such as *c-myc* are very important; *c-myc* is downregulated when the cells stop proliferation and differentiate, and its activation prevents cells from leaving the cell cycle, so that they have an increased potential for self-removal. In fact, *c-myc* mRNA transcript increases during stimulation of proliferation and decreases early in stimulation of differentiation. Tumor suppressor genes, such as p53, are now recognized to be of paramount importance in triggering tumor cell proliferation. Wild-type p53 inhibits cell cycle progression in G<sub>1</sub> by eliciting the production of a protein that blocks the progression of the cycle (cyclin-dependent kinases), and there is a downregulation of proliferating cell nuclear antigen (PCNA) mRNA and protein expression [2244]. Inactivation of p53, e.g., by mutation, by binding to protein of viral transforming genes, or by forming oligomeric complexes with MDM2, leads to cell proliferation. From the neuro-oncological point of view, the most important concept related to cell proliferation is that of growth fraction.

Cell proliferation increase leads to the increase of tumor growth fraction (GF). GF is an intrinsic characteristic of each neuro-oncotype, and the growth speed of the different brain tumors is well known. However, increasing GF within the same oncotype usually denotes progressive malignization.

GF, cell cycle time, population doubling time, and cell loss represent the basic factors regulating tumor growth. From the morphological point of view, the first signs accompanying anaplasia are an increased number of cycling cells and, consequently, an increase in cell density and/or tumor expansion. All the other histological parameters usually assumed to indicate malignancy, i.e., nuclear polymorphism, necroses, endothelial proliferations, can be regarded as being secondary to the in-

creased cell proliferation, even though some molecular mechanisms are now described as being responsible for their occurrence.

The first and simplest method to measure cell proliferation is to count mitotic figures, but it is also the least reliable method. The count may be expressed as the number of mitoses per high-power field (HPF) or per square millimeter. This method is sensitive to section thickness and cell size. More suitably, the count can be expressed as a percentage of mitoses after counting not less than 1000 tumor cell nuclei. The calculation of a mitotic index (MI) must also take into consideration other limiting factors: delayed fixation [398] and in particular the fact that the mitotic compartment accounts for the smallest proportion of cycling cells. However, mitotic counting remains an important method because of the low level of technology required. MI has been and is still widely used as a prognostic factor and can also be identified after multivariate analysis. An important remark must be made here and must be extended to any other method used to provide evidence of cell proliferation: MI has no intertumor validity as a prognostic factor; medulloblastoma has a MI higher than glioblastoma, but survives longer, and the same is true for oligodendrogliomas compared with astrocytomas.

One method which provided important information in recent decades, but is now obsolete, is autoradiography of tissue exposed to a pulse of [ $^3\text{H}$ ]thymidine [1403]. The same criticism made before is applicable to this method as far as intertumor validity is concerned. Medulloblastoma and glioblastoma are again an example. The potential radiation hazard of the [ $^3\text{H}$ ]thymidine method has been eliminated by the use of bromodeoxyuridine (BrdU), which is incorporated into DNA in S phase and can be immunohistochemically detected. A good correlation between the labeling index (LI) and histological malignancy has been described [1403, 1836]. BrdU can also be applied to fragments of tumor tissue incubated *in vitro*, with similar results [1937].

Cytophotometric analysis of DNA has not been reliable enough to evaluate minimal differences. Flow cytophotometry, based on the intensity of fluorescence emitted by a dye bound to the DNA [3510], is preferable. It has been demonstrated that the quantity of DNA is very variable in malignant gliomas where, beside diploid cells, there are many aneuploid or polyploid ones and many in S phase, while in benign tumors there are few cells in S phase, and the DNA content is more constant [954, 1406, 1617]. Obviously, the variations from one region to another of the same tumor are much greater in malignant tumors [1406]. On the basis of the DNA content, the various classes of cells have been found to be clonogenic [1408], and the variations genetic [1401]. Questions remain about whether clonogenic cell populations in culture correspond to the tumor cell populations *in vivo* [1401].

Flow cytophotometry may also be applied to tissues fixed and embedded in paraffin [1279, 1280]: Diploid elements prevail in differentiated gliomas, and aneuploid ones in malignant tumors [1068], although the percentage of the latter cells is not high [914].

Undoubtedly, it has been the development of autoradiographic techniques which permitted a more reliable definition of precise concepts such as the growth fraction (GF), doubling time of the cell population ( $t_d$ ), and cell loss factor (CLF). The GF corresponds to the proliferating pool of cells/total cell population [2235]. CLF has been calculated to be equal to  $1-(t_p/t_d)$ , where  $t_p$  is the potential doubling time [3289].

Autoradiography is carried out with the administration *in vivo* or *in vitro* of [ $^3\text{H}$ ]thymidine with or without the addition of mitotic inhibitors [3477]. The LI is the proportion of labeled cells. Over the years, fundamental contributions have been added [1545, 491, 1829, 993, 1404, 1407], revealing the LI to be high and greatly variable in glioblastomas (5%–15%), low in well-differentiated gliomas (1%), and intermediate in anaplastic astrocytomas (4%). These figures have been found to correlate with the survival data [1404]. The duration of the S phase ( $t_s$ ) has, in contrast, been noted to be constant (7–13 h), so that the turnover time ( $t_s/\text{LI} \times 100$ ) is a few days in malignant gliomas and about 2 months in astrocytomas. Calculation of the doubling time of a malignant glioma must obviously take into account the cell loss. Nevertheless, the autoradiographic method has not been exempt from criticism, some of which have even questioned its validity. In glioblastomas, for example, low values of LI have been found which do not correlate with survival [305]. The passage of [ $^3\text{H}$ ]thymidine through the blood vessels is one of these limiting factors, as are the extent vascularization of individual tumor areas and the possibility that thymidine binds to other substances within the tissue [2296].

More recently, a monoclonal antibody binding to DNA which incorporated BrdU has been produced [1157]. BrdU, a nonradioactive analogue of thymidine, may be administered *in vivo* with less damage than [ $^3\text{H}$ ]thymidine (Fig. 7.4a). The antibody labels DNA in the S phase, and it may be studied both in sections and with flow cytometry [2380]. The LI reflects the proliferative potential of tumors and correlates with survival [1413]. A good correlation has been found between data obtained by the examination of sections and those of flow cytometry [2381]. Tumors with similar histological features may have different proliferative potentials [1410, 1413], and a high LI may indicate a shorter recurrence interval in astrocytomas [1412], ependymomas [2381], and meningiomas [498, 992, 1479].

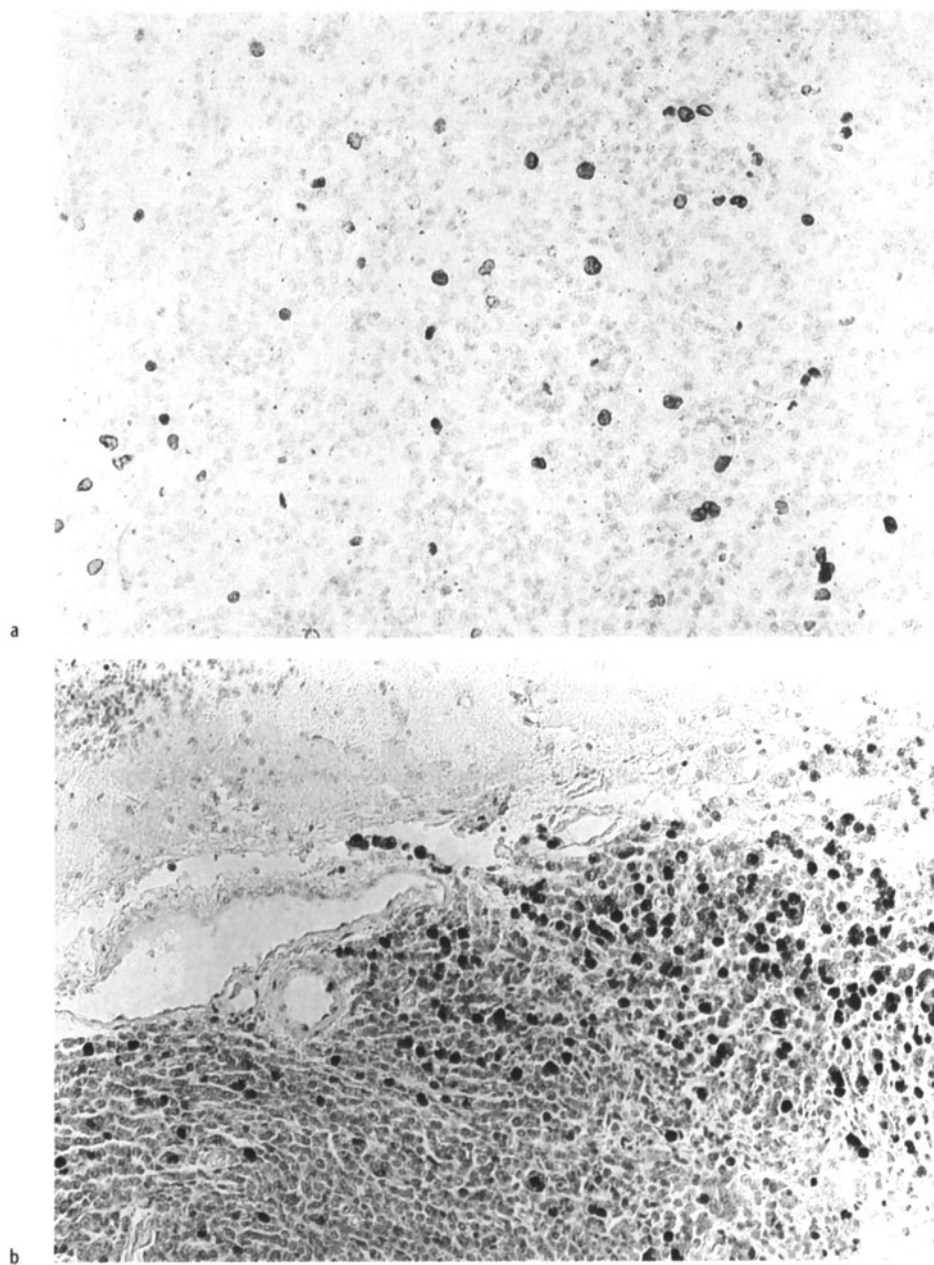
A method which may eliminate errors due to the variable vascularization of the tumor, avoids damage to the DNA with subsequent teratogenic effects [1409], and is of easier practical application is *in vitro* incubation of fragments of tumor tissue with BrdU [2322]. The method has given good results, similar to those obtained with other methods. However, due to the heterogeneity of malignant gliomas, it is advantageous to consider as representative of the tumor the area with the highest LI instead of making an average of the various areas [2322]. However, the possibility has been envisaged that an *in vitro* method entails the danger of overlabeling. However, LI calculated using *in vitro* methods were similar to those calculated *in vivo* [2252].

Undoubtedly, the BrdU method represents a good prognostic tool. Some limiting factors, however, must be taken into account such as the passage of the BBB, the diffusion of the antibody in the tissue, and the intensity of the immunohistochemical reaction. These factors could influence the results both positively and negatively, apart from the sampling errors common to all methods.

Using BrdU *in vivo* and iododeoxyuridine *in vitro*, it has been possible to measure the duration of S phase and the potential doubling time. A correlation has been found between BrdU LI and the other parameters [3166]. BrdU LI was also found to correlate with Ki-67 LI and DNA polymerase- $\alpha$  [3165].

Recently, the development of the monoclonal antibody to Ki-67 has opened up new avenues [1046]. It recognizes a nuclear antigen present in all phases of the





**Fig. 7.4. a** Labeled cells in an ethylnitrosourea (ENU)-induced tumor after in vivo administration of bromodeoxyuridine (BrdU), anti-BrdU. **b** Medulloblastoma, MIB-1-positive nuclei. PAP-DAB,  $\times 400$

cell cycle, except  $G_0$  [1047]. In brain tumors, the number of cells labeled correlates with histological malignancy (Fig. 7.4b) [395], even if the absolute values may vary from one study to another [1069], as in glioblastoma [695]. The method proved to be reliable and statistically significant through quantitative assessment, with differences in the LI among different malignant glioma [2711]. It has also been applied with success to stereotactic biopsies of gliomas [2518] and has demonstrated the presence of a high LI in recurrent or anaplastic meningiomas [2817]. A good correlation has been found comparing the in vitro administration of BrdU with Ki-67 [2322]. A nonlinear relationship between Ki-67 LI and MI was found in gliomas of different grades and meningiomas, which can be explained by the variability of cell cycle times [3072].

Many other contributions are available demonstrating the usefulness of Ki-67 method, with some limitations [217, 1512, 562].

Another antigen, p105, which is associated with proliferation has been tried. It is found in interchromatinic granules and is increased in proliferating cells [533, 534], but it does not seem to be useful for prognosis [914].

Another way to evaluate the proliferation potential of brain tumors is the visualization of nucleolar organizer regions (NOR) by the silver staining method. This demonstrates nonhistone proteins associated with NOR, which are sites of genes transcribing to ribosomal RNA. Their increased number and reduced size are considered signs of malignancy [712]. A study has been performed comparing the BrdU LI, Ki-67 LI, MI, and mean number of Ag-NOR/nucleus. A statistical correlation was not found among the different LI, probably because of technical difficulties in recognizing single Ag-NOR within nucleoli, especially in high-grade tumors [2075]. In another study [2655], the results were quite the opposite: The mean number of Ag-NOR per cell paralleled the degree of histopathological malignancy in gliomas. A relationship was also found between Ag-NOR and BrdU LI and survival, lending reliability to the method. Usually, Ag-NOR are studied on paraffin sections. Smear imprints seem to have some advantages over paraffin sections, rendering Ag-NOR more readily identifiable [2893]. With this method [1571], a close relationship was found with Ki-67 LI, and thus Ag-NOR technique may be considered suitable for estimating the proliferative potential of brain tumors, especially in stereotactic biopsies. AgNOR technique appeared to be simple and useful to distinguish between reactive gliosis and low-grade astrocytomas [2018]. In other studies, AgNoR was not as reliable as other proliferation markers [3166, 1820].

Another method recently introduced in practice is PCNA. PCNA cyclin is a 36-kDa protein auxiliary of DNA polymerase- $\delta$ . It increases in the cell through  $G_1$ , peaks in  $G_1/S$ , decreases in  $G_2$  and is virtually negative in the M phase. The gene for human PCNA is transcribed both in quiescent and proliferative cells, but PCNA mRNA normally accumulates only in proliferating cells. PCNA can be recognized immunohistochemically in formalin-fixed and paraffin-embedded material, and the distribution in non-neoplastic tissues is consistent with its association with cell proliferation. In non-CNS tumors it has been shown to correlate with Ki-67, flow cytometry, tritiated thymidine and BrdU incorporation.

One of the greatest advantages of this method, using clone PC10, is the possibility of a visual analysis by which the areas to be counted can be chosen. In addition, retrospective studies are feasible. Two factors are noteworthy: the broad spectrum of

staining intensity of nuclei and the high number of positive nuclei. These may be compared with the PCNA fraction not involved in DNA replication. The LI are higher than with Ki-67, which marks all the cell cycle phases. No tumors have a growth fraction as high as it would be after counting all the positive nuclei. Nevertheless, the ranges and the LI correlate with histological grade. Some limiting factors must be taken into account when evaluating PCNA staining: the titration of the method; the long half-life of the protein (20 h); the deregulation of PCNA in malignant tumors where its expression is dissociated from DNA synthesis; and the involvement of the protein in DNA repair.

A cutoff in the nuclear staining evaluation has been introduced, counting only very intensely positive nuclei [3035]; the figures become more comparable to those obtained with other methods, because intensely positive nuclei most probably represent S phase [463, 3035].

Recently, a new clone of Ki-67, MIB.1, has been applied to formalin-fixed and paraffin-embedded material. It seems to be highly reliable as a proliferation marker [1045], and some contributions on this subject have already been published [1592, 2504, 665, 3039, 1082].

The morphological and immunocytochemical markers of cell proliferation show different theoretical cell cycle distributions; thus their LI do not coincide. They roughly correlate with histological malignancy in the different tumor types, but their reliability as independent prognostic factors in individual cases is controversial. Some investigations led to negative conclusions [3795], whereas others identified a correlation only within certain limits [1512] or under specific conditions and in selected oncotypes [3035]. Recent investigations have demonstrated an association of LI of proliferation markers, especially of MIB.1, with the grade of malignancy and survival, but with a low reliability in individual cases [2934, 1420], or did not recognize them as independent prognostic factors [69].

S phase by flow cytometry and/or ploidy together with proliferation markers [564, 2934], however, showed a good correlation with the grade of malignancy. A positive correlation has been found between the duration of S phase and BrdU LI [3166] and between Ki-67 LI, DNA polymerase and BrdU LI [3165].

The factors responsible for the low reliability of LI as prognostic elements are as follows:

1. The methods employed indicate the state and not the rate of proliferation and they do not show the same reliability. They are not ideal.
2. Sampling error, which is common to all histological evaluations of malignancy in surgical samples.
3. The scoring method of labeled nuclei in relation to cell density.
4. Cell loss is difficult to evaluate quantitatively. Together with growth fraction, cell cycle time, and tumor doubling time, it represents a basic factor regulating tumor growth.
5. Heterogeneity for proliferation markers of tumors.

Tumor growth depends on the imbalance between growth fraction and cell loss. The latter can be calculated as CLF [3289] and is due either to necrosis or to apoptosis. Necrosis is the consequence of the imbalance between tumor proliferation and angiogenesis [3731] and cannot account for the high CLF observed in tumors [84],

whereas apoptosis is claimed to be the most significant component of the continuous cell loss in most tumors [3732].

Apoptosis can be, but is not necessarily synonymous with programmed cell death [3097]; it is typically found in embryonic tissues as a mechanism by which a variety of cell types are deleted during development [580]. It also occurs in adult tissues with a high cell turnover and in malignant tumors, in which it is associated with the control of cell proliferation. Apoptosis is regulated by the same oncogenes and proteins that regulate cell proliferation: *c-myc* expression, p53, and *bcl-2*. Morphologically, apoptosis is characterized by chromatin condensation against the nuclear membrane, nuclear blebbing, chromatin splitting, and formation of apoptotic bodies. The cell is finally phagocytosed by macrophages. The biochemical events are the  $\text{Ca}^{2+}/\text{Mg}^{2+}$ -dependent activation of endogenous endonuclease, leading to cleavage of chromatin into oligonucleosome-length DNA fragments, as shown by DNA "laddering" on agarose gel electrophoresis. Oncogenes regulate the availability of  $\text{Ca}^{2+}$  and up-system protease activation [2205]. Another step consists in tissue transglutaminase, a  $\text{Ca}^{2+}$ -dependent enzyme, catalyzing the formation of protein cross-links by an acyl-transfer reaction.

The regulation of cell proliferation and apoptosis by the above-mentioned oncogenes and tumor suppressor genes is complicated; *c-myc* may produce either cell proliferation or apoptosis, depending on the availability of critical growth factors [853]. Three extreme states can be envisaged: (1) growth arrest with downregulation of *c-myc* and absence of growth factors, (2) population expansion with upregulation of *c-myc* and growth factors present, and (3) apoptosis with upregulation of *c-myc* and growth factors absent [3733]. An intermediate "high-turnover state" may exist with high susceptibility to enter apoptosis or cell cycle. Wild-type p53 arrests cells in  $G_1$  prior to mitosis (checkpoint 1), whereas its inactivation favours proliferation; *bcl-2* inhibits apoptosis.

The regulation of apoptosis is a highly complicated mechanism involving different molecular events. One of these involves Fas antigen or APO-1, which is a member of the tumor necrosis factor (TNF)/nerve growth factor (NGF) family. Its activation induces apoptosis. However, Fas/APO-1 requires activation of a new class of cysteine proteases, including interleukin-1 $\beta$ -converting enzyme (ICE), homologous to the product of *Caenorhabditis elegans* cell death gene *ced-3* [3764]. Conversely, inhibition of ICE suppresses Fas-induced apoptosis [2010]. A gene encoding another ICE-like protein, CPP32, has been cloned [885], and a cysteine proteinase resembling ICE, prICE, has been detected in extracts from cells committed to apoptosis [1888]. Other events involved the activation of Ras, which may be involved in suppressing apoptosis; Ras activation can be promoted by stimulation of guanosine triphosphate (GTP) exchange from receptors containing tyrosine kinase domains [2205, 2225]. Cellular immediate-early gene (cIEG) response precedes cell death in vitro and in vivo [489]. These are mainly *c-fos* and *c-jun*, which can be shown by fusing them with *lacZ*, which encodes  $\beta$ -galactosidase, which in turn can be demonstrated.

Apoptotic nuclei can be demonstrated in brain tumors morphologically, by cationic dyes, or by electron microscopy, based on the characteristics of their chromatin or by in situ end-labeling of DNA breaks using conjugated nucleotides with digoxigenin and terminal transferase (ISEL technique) or polymerase. On formalin-fixed material, the technique gives good results [2262]. Apoptotic nuclei have been demon-

strated in medulloblastoma [3037] and in other neuroepithelial tumors. The apoptotic index (AI) is high in embryonal tumors and low in differentiated tumors. It correlates with MI, but not with survival [3039a]. It has been considered a possible prognostic factor [2980]. However, in other studies, it has been found to correlate with Ki-67 LI, but not with p53 or *bcl-2* [820]. The correlations among all these factors might be too complex to be demonstrated in tissue sections. In astrocytic tumors, the degree of *bcl-2* expression has been inversely related to the degree of malignancy, but no relationship was found with survival in glioblastomas or medulloblastomas [2395]. In our series, *bcl-2* was highly expressed in medulloblastomas and astrocytic tumors, with no correlation with survival and, therefore, of no prognostic value [3040].

Fas has been immunohistochemically demonstrated in 70% of gliomas, where it correlates with apoptosis, whereas *bcl-2*, *bcl-x*, and *bax* were positive in 71%, 56%, and 37%, respectively, in malignant brain tumors [3173]. By reverse transcriptase polymerase chain reaction (RT-PCR), Fas mRNA was found to correlate with malignancy [3368].

### 7.3

#### Metastasis

Distant dissemination in the rest of the body (metastasis) is different from seeding within the CNS via the CSF. The former is a rare event for brain tumors. For a number of years the occurrence of well documented examples of blood borne metastases of gliomas was a matter of debate. Beside completely negative positions [3696, 3799], others used less restrictive criteria in the documentation of cases [604, 2899]. The absence of lymphatic vessels in the CNS, the protection of large veins, the collapse of small veins, the impossibility of growth of neural tissue elements in other tissues, and the short survival of patients with malignant gliomas were reasons given to explain the absence of metastases [3686]. Criteria were developed on the basis of which the reported cases could be accepted. These are as follows [3637]:

1. The histologically demonstrable presence of a neuroepithelial tumor in the CNS
2. Concomitant and relative clinical symptoms
3. Histological characteristics of metastases similar to those of the primitive tumor
4. Negative autopsy findings for tumors in other organs

An analysis of the literature up to 1961 made with these criteria led to the identification of 81 cases, but not all of them were considered to be acceptable [1946]. There were no doubts, for example, of metastases to bone from medulloblastoma; and to cervical and supraclavicular lymph nodes and lung from ependymomas and glioblastoma [858, 2994]. Metastases were also found for mesodermal tumors, such as meningiomas and sarcomas.

The old considerations on the absence of remote metastases [3686] have been demonstrated to be unfounded. Even though there are no true lymphatics in the CNS, a CSF lymphatic drainage system exists, both under normal conditions and during increased intraventricular pressure [2195]. The veins may be invaded by the tumor [2333], and the tumor cells may grow extracranially. It has, in fact, been demon-

strated that autotransplants of anaplastic astrocytoma in subcutaneous tissue may grow successfully with a morphology similar to that of the original tumor [171]. It is, however, obvious that, due to the inexpandibility of the cranium, a brain tumor cannot reach the same mass as an extracranial tumor without being fatal, and this limits the possibility of metastases [54]. There are, however, exceptions facilitated by craniotomies, which favor the diffusion to soft tissues and hence to lymph nodes [2903], even though some maintain that this is not essential [77, 325].

Until late 1985, 282 metastatic cases had been reported. Forty per cent were in children, mostly medulloblastomas, followed by astrocytic tumors, ependymomas, and meningeal tumors. In the adult, astrocytic tumors prevailed, followed by meningeal tumors, medulloblastomas, and ependymomas [1365]. Medulloblastoma metastasizes to bone, bone marrow, lymph nodes and, less frequently, to lung, pleura, liver, and breast. Glioblastoma and ependymoma metastasize to the lungs, less often to bone, pleura, and liver. Meningiomas metastasize to lung and pleura, less often to lymph nodes, liver, and bone.

Metastasis is not always accompanied by local recurrence, and there are even cases in which the primitive tumor was not found at autopsy [1709].

With the employment of CSF shunts, cases of metastasis have increased. Of the 282 cases of metastases mentioned above, 34 had a shunt, and 33 of these were in children [1365]. However, with the exception of malignant pineal tumors, this is not universally accepted. The use of a Millipore filter in these shunts seems to have reduced the possibility of metastasis [2559].

The relatively high incidence of extracranial metastases in children can also be explained by their longer survival due to the improved treatment, and by immunodepression following chemotherapy [777].

The rarity of glioma metastases had also been explained by their growth along the lines of lesser resistance, with a tendency to infiltrate the perivascular spaces rather than penetrate the blood vessels. This was supported by experimental studies [3786, 2403]. Collagen IV studies demonstrated that the endothelial cells, rather than the basement membrane, form a barrier to tumor infiltration. The possibility that tumor cells may enter the blood vessels from the perivascular space [1819] is not generally accepted [1330, 3644]. Vessel penetration, dissemination through the systemic circulation, passage of the cells into the target organ, and the formation of micro- and macrometastases with neovascularization form the steps of the entire process [1990].

Seeding via the CSF is, on the contrary, frequent enough. Metastases may be near or distant to the primitive tumor and single, multiple, or diffuse, as in the "secondary meningeal sarcomatosis." Apart from medulloblastoma, which more frequently than other tumors gives rise to diffuse dissemination, the neuroepithelial neoplasms usually seed along the CSF routes [3799]. Spinal metastases can be found in all neuroepithelial tumors pilocytic astrocytoma included. In ependymomas, for example, the percentage of subarachnoid metastases is high, especially if the tumor is in contact with the CSF pathways. Metastases have even been found from tumors primarily located in the region of the cauda equina [2181]. These latter are tumors which are repeatedly surgically treated, with long survival and massive local recurrence.

Very rarely, the metastasis produces clinical signs before the primary tumor, or its symptoms are so dominant as to require surgical intervention first [522, 3348].

Under the name of “meningeal gliomatosis” are included gliomas with diffuse dissemination to the meninges. The 42 tumors described by Polmeteer and Kernohan [2662] were subdivided as follows: 20 medulloblastomas, six glioblastomas, five ependymomas, five oligodendrogliomas, three astrocytomas, two retinoblastomas, and one pinealoma.

Leptomeningeal diffusion is particularly frequent for neuroepithelial tumors in children, where it may occur in 10%–20% of cases [89, 2527]. It has been found in 43% of malignant gliomas, in 27% of medulloblastomas, and in 15% of germ cell tumors. These figures are greater than those found in adults [3490]. Recently, the number of cases with meningeal gliomatosis in children has increased further, probably due to the improved survival of neuroepithelial tumors after craniospinal radiotherapy. It has been calculated to occur in 50% of medulloblastomas and in malignant gliomas [2530]. Studies in progress tend to see the process of diffusion as regulated by mechanisms of exfoliation, adherence, and cell conglutination [2156].

## 7.4

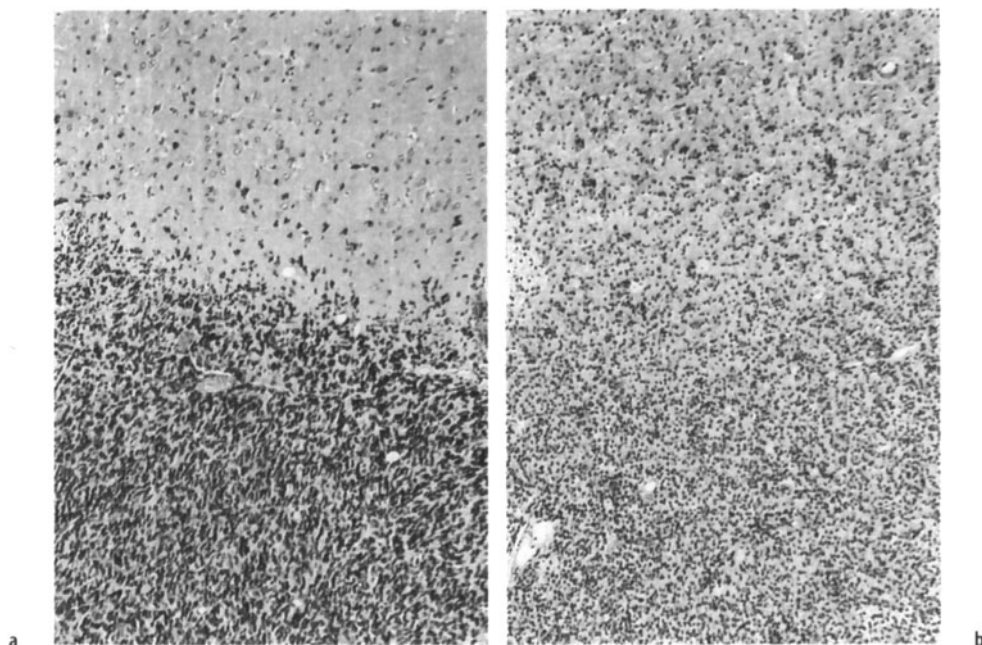
### Expansion and Invasiveness

Brain tumors grow by expansion or infiltration. Expansion may or may not be accompanied by encapsulation. Neurinomas, pinealomas, teratomas, and meningiomas are fully or partially encapsulated; the capsule, in these cases, does not continue over the dura and fails to prevent invasion of the meninges. Angioblastomas, choroid plexus papillomas, and ependymomas are not encapsulated. They push aside the nervous tissue, which may undergo atrophy and gliosis. In ependymomas, for example, there may be a distinct border between the tumor and the nervous tissue, but this does not preclude infiltration elsewhere. This is true also for oligodendrogliomas (Fig. 7.5a). Pineal region tumors, particularly germinomas and pinealoblastomas, grow over the lamina quadrigemina but eventually invade the posterior part of the third ventricle and reach the intermediate commissure, or even the foramina of Monro. The thalami are pushed aside, the posterior part of the corpus callosum upwards, and the vermis downwards and backwards. All these structures may be infiltrated as well.

Growth by infiltration is typical of gliomas but is also observed in other tumors. It may be circumscribed or diffuse [425]. Local and circumscribed infiltration is typical of cerebellar and midline astrocytomas, oligodendrogliomas, and glioblastomas, whereas diffuse infiltration is associated with astrocytomas, glioblastomas, medulloblastomas, oligodendrogliomas (Fig. 7.5b), and malignant lymphomas. The limits of the tumor cannot always be established histologically, since its cells are intermixed with normal and reactive cells. Infiltrative growth in one place does not exclude sharp edges of the tumor in other areas.

The spreading capacity of neuroepithelial tumors is largely due to their growth potential and invasive behavior. Invasiveness depends upon many factors, among which are certain biological properties. *In vitro* studies have shown that the fibrinolytic activity [3772, 1321], phagocytic activity of glioma cells [2459], and high migratory capacity [2666, 1263] are important with regard to invasiveness [1840].

In relation to the invasion capacity of neoplastic cells, some characteristics, such as migration and adherence [1711, 2892] have to be taken into account. For example,



**Fig. 7.5a,b.** Anaplastic oligodendroglioma. **a** Clear-cut delimitation of the tumor. **b** Progressive infiltration of the cortex. (From [2994]). H&E,  $\times 200$

the cellular proliferation may be influenced by many proteins of the extracellular matrix [35]. These are especially involved in the interaction between tumor cells and host tissue [1973]. Observations on experimental tumors demonstrate that tumor invasion is related to the synthesis and degradation of proteins of the extracellular matrix [2889].

However, though the biology of tumor invasion remains largely unknown [3600], it has been compared with angiogenesis, with which it shares such characteristics as a high copper content [3784]. In the 9L gliosarcoma cell line transplanted into the rat, a copper-poor diet and penicillamine treatment inhibit pseudopodial protrusion [327]. It is clear that invasiveness and infiltration are not identical, and that the latter is not a synonym for malignancy. It should be pointed out that the idea that expansion is typical of benign, and infiltration of malignant tumors would imply that diffuse astrocytomas are malignant, as once believed [2984]. The main difference between the spread of slowly growing hemispheric and malignant gliomas is that the former are often diffuse, with no sharp demarcation, whereas the latter grow both by expansion and infiltration.

The way a tumor spreads is greatly influenced by the existing structures and by the general anatomy of the structure in which growth takes place. If a tumor grows in a ventricle, i.e., ependymoma, plexus papilloma, or medulloblastoma, or reaches it from the parenchyma, as oligodendroglioma, glioblastoma, and germinoma often do, the cavity may be filled. This has been called “plastic” ependymoma with regard, for example, to intraventricular ependymoma.



Growth out of the ventricle is exemplified by the passage of ependymoma from the fourth ventricle to the subarachnoid spaces through the foramina of Luschka. A tumor may also spread from one cavity to another. Pineal tumors, for example, pass from the third ventricle to the lateral ventricles through the foramina of Monro. A tumor can reach the subependymal layers and grow into them, with or without protrusion into the cavity. It may also spread into the ventricular system and the subarachnoid space (Fig. 7.6).

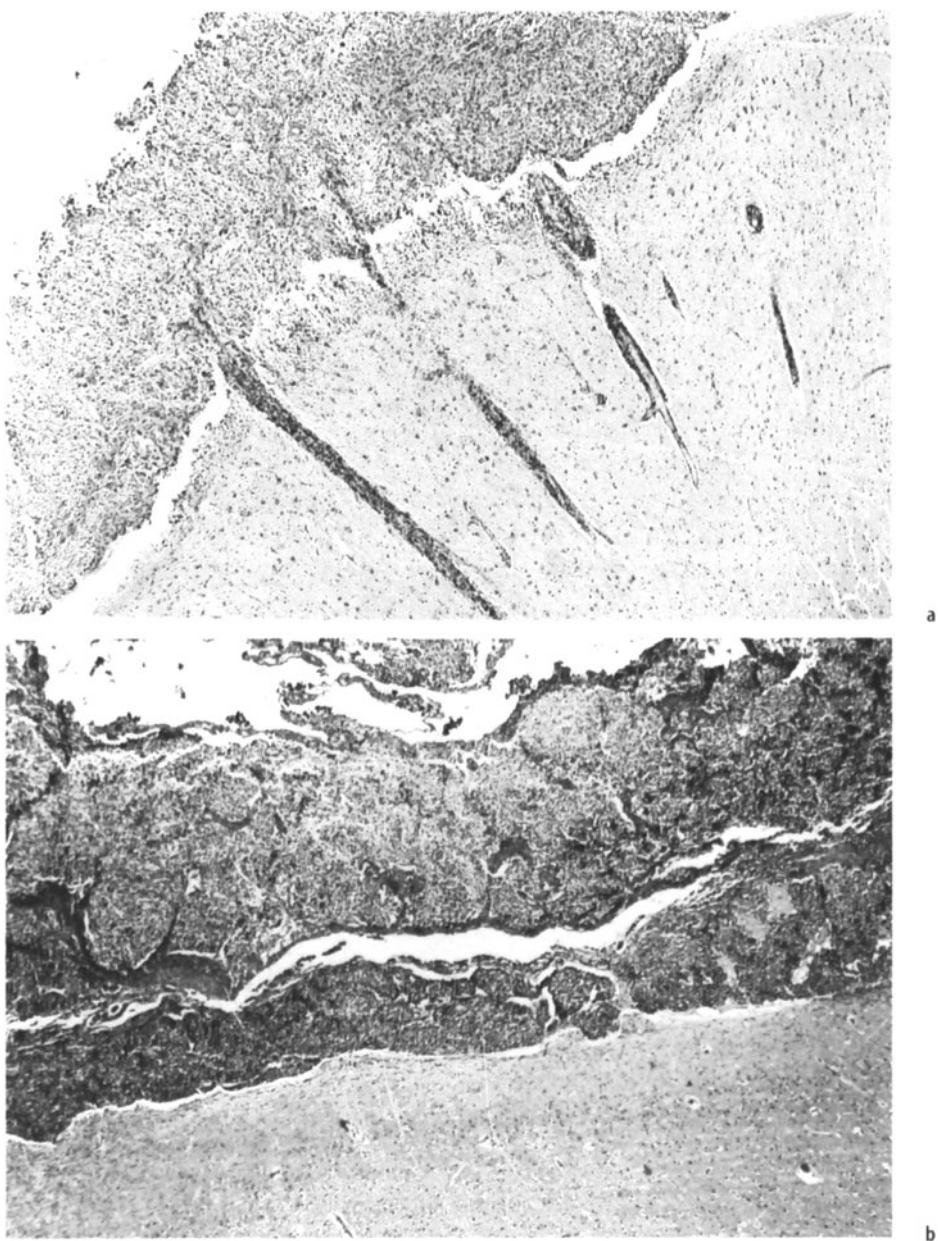
If tumor cells find their way into the CSF, metastasis can be retrograde as well as along the spinal cord. Medulloblastoma, ependymoma and glioblastoma are mainly responsible for this kind of colonization. Metastases can be found on the arachnoid, among the posterior roots, and in the cauda region. These observations have guided the strategy of radiotherapy which is applied to the entire neuraxis in cases of medulloblastoma and ependymoma.

A tumor can also spread in the cortex and along its outer surfaces. A glioma growing from the white matter to the cortex has several pathways which it may follow: invasion of the cortical layers, thus creating the appearance of satellitosis (Fig. 7.7), although the neurons themselves may remain visible for a long time; crossing the pia and giving rise to subpial and leptomeningeal growths, from which the cortex itself may be reinvaded; expansion into the leptomeninges resulting in meningeal gliomatosis [2662], leaving the gyri either normal or invaded, as seen when oligodendrogliomas infiltrate convolutions and give them a "hypertrophic" appearance. As they pass from one convolution to another, the tumor produces "garlands" by forcing a passage through the cortex in the same way as a fungus.

One of the main routes along which hemispheric gliomas spread are the fiber tracts, i.e., the corona radiata, internal capsule, corpus callosum (Fig. 7.8), and anterior commissure [2157]. Gliomas have typical sites of origin, which become less recognizable during tumor growth. The spreading pattern depends on the location and is schematically predictable [425]. Progression is both in the ipsilateral hemisphere and through the corpus callosum to the opposite side, giving rise to the classic picture of a "butterfly" tumor.

Histologically, elongated cells are observed among the myelin fibers. They acquire a pilocytic or spongioblastic appearance, since their growth pattern is greatly influenced by the existing fiber plane. It is often difficult to determine whether they represent a primary or a secondary architecture. When the cell density is low, it is even difficult to recognize the advancing tumor. This growth pattern is shared by glioblastomas and different types of hemispheric and midline pilocytic astrocytomas.

Malignant gliomas very often present as multicentric growths (see Fig. 9.14) or as a multicentric malignant transformation of a diffuse astrocytoma. The first possibility raises serious difficulties in the differential diagnosis of metastasis by CT scan (Fig. 7.9). The multifocality of a tumor is an event difficult to prove since in most cases it is merely apparent. The multiple foci may be connected by thin strips of tumor involving commissures or septa, such as the septum pellucidum. In other cases, multifocality may be mimicked by diffusion through the CSF followed by reimplantation. The second possibility is that an astrocytomatous proliferation, not detectable by CT, may connect all the foci visible on CT into a single large, tumor [1960]. This situation is of great importance when it is necessary to establish the extent of a tumor by CT so that an appropriate radiotherapy strategy may be chosen [2990, 389].



**Fig. 7.6. a** Subarachnoid seeding of a glioblastoma with reinvasion of the cortex. **b** Proliferation of an oligodendroglioma in the subarachnoid space. H&E,  $\times 150$

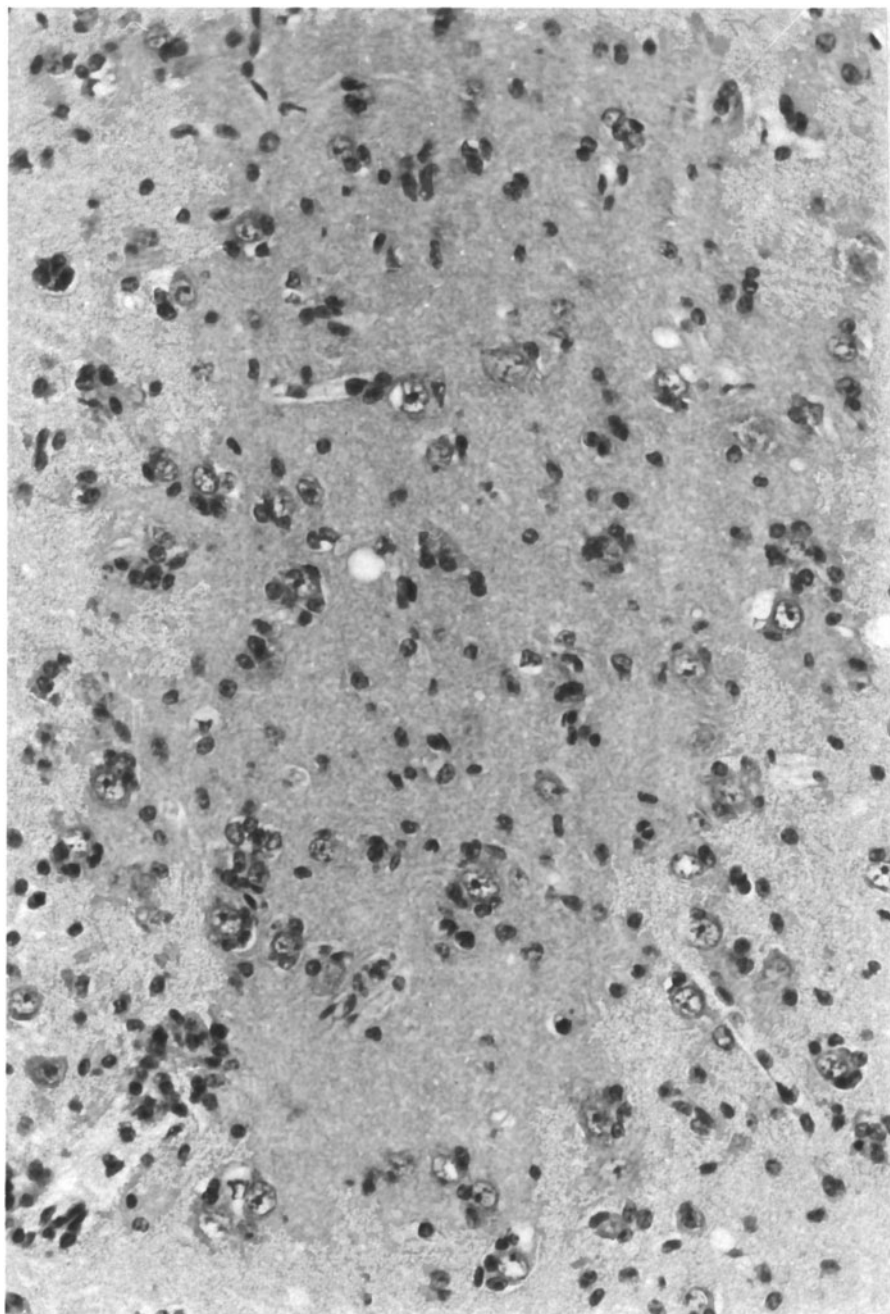


Fig. 7.7. Perineuronal satellitosis in an oligodendroglioma. H&E,  $\times 300$

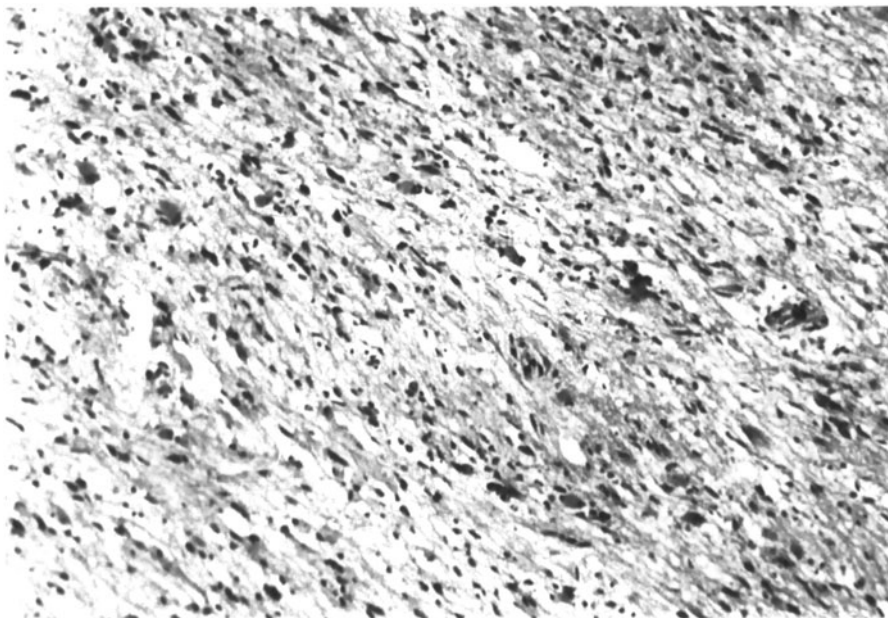


Fig. 7.8. Spreading of a glioblastoma into the corpus callosum. (From [2994]). H&E,  $\times 200$

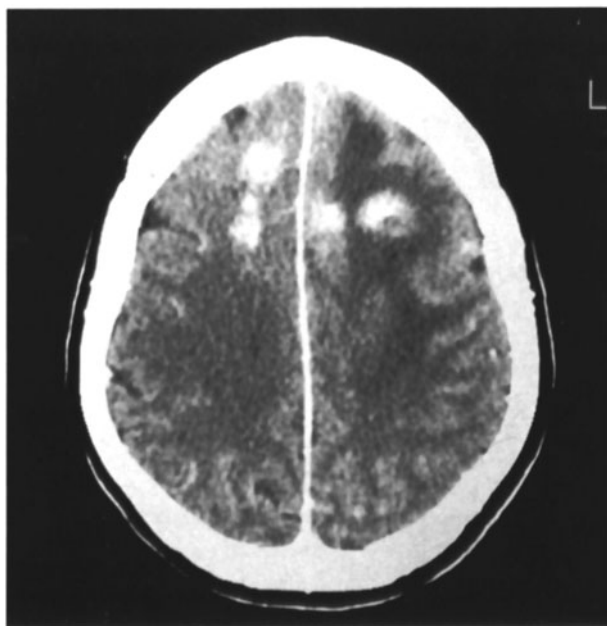


Fig. 7.9. Apparent multi-centric growth of glioblastoma on magnetic resonance imaging (MRI)

There is also the possibility of a transdural extension of gliomas in patients not operated on. This may happen in anterior and middle cranial fossa through basal foramina, along vessels and nervous trunks [1990, 3222], or to the orbit. The extraneural extension may be realized through perforation of dura and bone [2665]. Obviously, this extension is quite common after operation.

#### 7.4.1

##### Invasion Mechanisms

Tumor cell invasion includes cell migration, i.e., cell motility and the capacity to modify the environment. In addition to what is known from human pathology, a great deal of information on these matters has recently been obtained using animal and in vitro models. The former, consisting mainly in transplantable gliomas and ethylnitrosourea (ENU)-induced tumors, have a series of disadvantages, such as high proliferative rate [2645] and metastatic capacity [65], which make them barely comparable with human brain tumors. The latter seem to be more suitable for the study of cell motility and invasion capacity. Different types of experiments have been carried out, with different models. One is the three-dimensional confrontation with normal tissue and neoplastic glia cells [681]; another one involves the interaction between glioma cells and fetal rat brain aggregates [261]. One of the more sophisticated techniques uses "Transwell units" [863].

A role of paramount importance in cell invasion in most organs and tissues is played by extracellular matrix (ECM). This is composed by collagens, fibronectin, laminin, entactin, elastin, tenascin, vitronectin, chondroitin sulphate (CS), hyaluronic acid (HA), and heparan sulfate (HS) proteoglycan. It is generally acknowledged that the interaction of tumor cells with ECM is accomplished in three steps [1974]: (1) adhesion to ECM, (2) degradation of ECM, and (3) locomotion. Adhesion of tumor cells to the ECM is mediated by a variety of transmembrane receptors such as integrins and cell adhesion molecules (CAM). Changes in many of these receptors accompany malignant transformation [696]. The family of membrane glycoprotein CD44, expressed by astrocytes [1084], is the major receptor of HA, which is produced by astrocytes. The hydration of HA causes extracellular spaces to open up, permitting the entry of invading cells [1726]; these release hyaluronidase, which breaks down HA. CD44, therefore, mediates cell-ECM interaction. Distinct forms of CD44 arise from alternative RNA splicing and are functionally different [1198]; variant CD44 is expressed in human brain metastases, but not in glioblastomas [1948]. Neuroepithelial tumors express only the standard CD44 [2375].

Gangliosides have been shown during development to be highly expressed by migratory cells [3225], and they are thought to be associated with migration of tumor cells. Since cells expressing gangliosides, for example A2B5, are not labeled with PCNA or BrdU [2642], it has been supposed that tumor cells transiently leave the cell cycle during migration. However, gangliosides added to human glioma cell lines inhibit proliferation and stimulate invasiveness [2646].

Many growth factors have been suggested to be involved in invasive activity, e.g., epithelial growth factor (EGF) and basic fibroblast growth factor (bFGF), as well as some new cytokines such as autocrine motility factor (AMF) and migration stimula-

tion factor (MSF). The receptor of the former might be a novel HA receptor [2369], whereas the latter might stimulate the high molecular weight form of HA [3084]. Another factor which plays an important role in malignant progression of human gliomas, strongly antimitogenic transforming growth factor (TGF)- $\beta$ 1, has been shown to stimulate ECM formation and modulate cell adhesion and migration [2142]. In vitro, it elicits a strong stimulation of migration and invasiveness of glioma cells [2248]. Other factors regulating cell invasion are a group of Zn-dependent endopeptidases, the metalloproteinases (MMP), including collagenase, gelatinase, and stromelysin [2150]. MMP are regulated by their inhibitors, tissue inhibitor of metalloproteinase (TIMP), and by TGF- $\beta$ , EGF, and bFGF; they have been demonstrated in the CNS, although their role is obscure [2890, 78, 2074]. Several types of MMP inhibitors have been described and are known as TIMP-1, TIMP-2, and TIMP-3; there is increasing evidence that they act as suppressors of tumor invasion and metastasis [3432]. Overexpression of 18A2/mts1 and downregulation of TIMP-2 play an important role in the invasive behavior of human glioma cells in vitro [2249]. MMP have been demonstrated in invading C6 glioblastoma [2536], and TIMP-2 has been shown to reduce the blood-brain barrier (BBB) opening by collagenase [2834]. The regulation of MMP and their inhibitors is very complicated and involves many cell molecular functions [2823]. Many other proteinases are involved, such as cysteine proteinases, cathepsin B and L, and aspartic proteinases, such as cathepsin D [672]. Cathepsin B has been described in brain tumors; it is found at the tumor edge, where local invasion occurs [2764]. Other enzymes involved in ECM degradation are plasminogen activators (PA), a family comprising two members: urokinase-type PA (uPA) and tissue-type PA (tPA). Once activated, they cleave plasminogen to plasmin, which acts as a serine proteinase in different substrates such as fibronectin and laminin. There are also PA inhibitors (PAI-1 and PAI-2) [2823].

High levels of uPA have been found in glioblastoma [1857, 1037]. Using antibodies against uPA receptor, an inhibition of invasiveness of glioblastoma cells has been observed; uPA receptor probably facilitates uPA activity [2294]. A considerable body of literature has now been published on PA in brain tumor growth and invasion [3432], and a further demonstration that antibodies to serine proteases inhibit invasion rate in vitro has been given [2731].

In addition, a series of genes have been associated with invasion [3310]; 18A2/mts1 gene is involved in metastatic potential [2560], as is nm23 [1845].

In the CNS, the ECM has been identified in three main structures [2910]: (1) the glial limitans externa, composed of collagen types I, III, and IV, fibronectin, laminin, and CS proteoglycans; (2) basement membranes, composed of type IV collagen, laminin, entactin and HS proteoglycan; and (3) brain parenchyma, of which HA is the main component [236]. ChS proteoglycans are also present and are capable of binding HA [1077]. Hyaluronectin, a glial hyaluronate-binding protein (GHAP), has been described as being produced by astrocytes [239]. It is important to emphasize that glycosaminoglycans have been demonstrated to be increased in brain tumors at their interface with the normal nervous tissue [220, 1097]. In this regard, the role played by HA during migration of neural crest cells must be kept in mind [2943].

## **Descriptive Epidemiology of Primary Nervous System Tumors**

### **8.1 General Data**

#### **8.1.1 Mortality**

Data pertaining to the mortality of patients with primary CNS tumors are readily available, as many countries have published the standardized data collected through death certificates. Comparison between mortality rates (number of deaths/100 000 inhabitants per year) of various countries in the periods 1951–1958 [1118] and 1967–1973 [124, 125] has shown a persistent geographic variability and a clear tendency to increase with time. The annual age-adjusted rates for the period 1951–1958 varied from 1.1 (Mexico) to 6.8 (Israel), while for the period 1967–1973 they varied between 4.2 (Chile) and 10.0 (Federal Republic of Germany). For the majority of countries the increment in mortality rates was about 40%, although it was over 100% in some. The increments were lower and of the same magnitude in countries with high health standards before 1958 (United Kingdom, United States, and Canada). The increase in mortality with time was found to be particularly high (from 5.3 to 16.1) when white Americans between 60 and 64 years born in 1880 and 1910 respectively, were compared, while in younger subjects this increment was not found [267]. This observation led to the belief that the increment in mortality over time for CNS tumors is mostly related to improvements, variable from country to country, in the social/health systems, diagnostic facilities, and data collection [2291].

Mortality is higher in males than females. Still referring to the 1963–1973 period, it has been noted that the mortality rate was about 7.5/100 000 for males versus 5.58/100 000 for females [3075]. In Italy, the values were, respectively, 4.86 versus 3.66 in 1956 and 6.76 versus 4.92 in 1978 [669]. The mortality curve in relation to age demonstrates a modest peak in infancy, followed by a higher peak in adults [1118, 1828]. The mortality for CNS tumors was higher in whites than in other races [1828].

#### **8.1.2 Incidence**

Data on the incidence of primary CNS tumors collected in tumor registries from 30 different populations through the UICC relating to the 1968–1977 period [125] reveal many analogies with mortality data. There was, in fact, marked geographic variabil-

ity: the incidence rates adjusted for age (number of new cases/100 000 per year) varied from 1.5 (Singapore) to 9.1–10.0 (Israel and Sweden). The values were high, with minor variations in time, for countries with a high socioeconomic status and generally higher in males (male to female ratio, 1.3). The increase in incidence with time has clearly been lower than the increase in mortality. There had even been a decrease in one third of the countries.

The race differences heavily influenced the incidence ratio. In multiracial communities, such as the United States, for example, the incidence was constantly higher for whites than for Indians and blacks. For a given race, instead, there were no differences between natives and immigrants from other countries. Differences in ethnic origin may also be important: Within the Israeli population, the incidence of malignant primary tumors varied between 14.3 for Hebrews born in Europe or America to 9.5 for those born in Israel.

## 8.2

### Epidemiology of Intracranial Tumors

Data relating to the epidemiology of intracranial tumors alone are of two types: those based on a hospital series (neurosurgical and neuropathological) and those based on population studies. The first type arises from carefully collected series as for the classification of tumors but are often “selective,” i.e., influenced by the specialization of various centers. The second has the advantage of deriving from studies in which the frequency was calculated for the whole population “at risk” but was often limited by a less accurate histological diagnosis, because these included nonhistologically verified cases. The frequency of cerebral tumors found in autopsy series is about 1.2%–1.4% [2994].

The incidence ratio of primary intracranial tumors varied from 4/100 000 in Iowa, USA [1213] to 14.7/100 000 in Rochester, Minnesota, USA [72, 1824]. These enormous differences are in part artifactual and reflect the diversity in the definition and in the methods of case ascertainment. Some studies do not consider tumors of the pituitary gland [545] or include spinal tumors [151]. In general, higher values are related to more accurate case ascertainments, as found in isolated small populations with little mobility and high health care standards such as the Faroe Islands or Rochester [1542, 1824]. They can be found also in more recent studies using computed tomography (CT) in the diagnosis [921, 3344, 631]. The particularly elevated values found in Rochester are for the most part due to the inclusion of cases diagnosed only at autopsy [3073]. If these are excluded, the maximum frequency ranges from 9.5 (1950–1969) to 12.5 (1970–1989) [2702], which is not significantly different from the 8.5 average value reported for the United States [3593]. In large studies carried out in Connecticut [3077] and Rochester [72], the increase in incidence over time was attributed to better case detection. Italian data vary from 8.4 or 8.5 in the Trento and Bolzano provinces [2024, 2006] to 9.2 in the province of Varese [2778].



### 8.2.1

#### Histological Type

The distribution according to histological types of primary intracranial tumors overlaps uniformly (with few exceptions) in population studies and clinicopathological series. Gliomas rank highest (40%–67%), almost always representing more than half of all tumors, followed by meningiomas (9%–27%), on average about 20%, and then pituitary adenomas (7.6%–14%) [3593, 3075]. An exception is the Rochester study [1824], in which meningiomas (40%) were more frequent than gliomas (35%). However, if only cases diagnosed ante mortem are considered, the percentages are closer to those of other studies. The interest which neurosurgeons and neuropathologists have for particular oncotypes has led to a higher frequency of some tumors in some series, as in the case of pituitary adenomas for Cushing [2319] and meningiomas for Olivecrona [2353]. Particular distributions are probably influenced by genetic-racial and/or environmental factors as, for example, the high frequency of acoustic neuromas in India [650] or of pineal tumors in Japan [81].

Within the glioma series, the most frequent oncotype is glioblastoma (more than half), followed by astrocytoma and ependymoma. The incidence rate values vary from 2.1 to 7.1/100 000, with a tendency to higher values between 4 and 6 in more recent studies [1289, 1574, 2949, 1288, 1925]. Within the subtypes of gliomas [3074], the following figures were reported: for astrocytoma 0.52 in males and 0.34 in females, for glioblastoma 2.07 and 1.51, and for ependymoma 0.08 and 0.07, respectively. From the brain tumor registry of Japan, gliomas represent 28.9%. The oncotype distribution is astrocytoma 43.1%, medulloblastoma 7.3%, glioblastoma 26.6%, oligodendroglioma 6.1%, ependymoma 6.3%, and plexus-papilloma 1.2% [2450].

### 8.2.2

#### Age

Many studies demonstrate a first incidence peak in infancy, with a subsequent, more marked, peak in the decade 55–65 years, followed by a decrease, especially after the age of 70 years. In the Manitoba Canadian epidemiological study [3344], the incidence was 4.2/100 000 in the 0- to 4-year group, and 27.2/100 000 in the 60- to 69-year group. The only exception was reported in the Rochester study [1824], where the incidence was found to continue to increase even after the age of 65 and 70 years. This finding was relevant only for gliomas and meningiomas diagnosed at autopsy. It is possible [3593] that when studies based on routine CT scans become available, the incidence curves for age may become closer to those of the Rochester study. Even today, they have reduced the number of undiagnosed tumors in vivo, especially in the elderly. A bimodal shape of incidence curves for age, similar to that of intracranial tumors globally considered, has been observed for gliomas, but with different shapes for different oncotypes. Well-differentiated astrocytomas and ependymomas account for the peak of gliomas in the infantile age, and in adults their incidence shows a relatively flat and regular curve. The incidence of glioblastomas, relatively rare in the younger age group, follows a steeply ascending curve from 30 years onwards, with a

nadir around the age of 65 years. Oligodendrogliomas occur fairly constantly at all ages, with a slight predilection for middle age.

Brain tumors in childhood (0–15 years), considered as a separate group, have an incidence of 2.2–2.5/100 000, varying between 1.0 and 5.0/100 000 [3078, 1112, 2567, 2682, 1865]. The incidence is always inferior to that of tumors in adult age. The peak incidence is between 3 and 9 years of age [1935]. There is no qualitative difference in oncotypes as compared with adults.

As the renewing reserve cells, the neuroepithelial cells are scarce and the turnover of glia is low in the adult CNS, it may be thought that the majority of gliomas originate because of neoplastic transformation of neuroepithelial cells during development. It follows that there is no difference between tumors of adult and embryonal type, as encountered in other organs [2876]. Very enlightening in this respect is the application of the concept of “window vulnerability” [2876] referred to in Chap. 7.

Cerebral tumors are very rare in the first 2 months of life and account for 1.5% of all brain tumors in infancy [2955, 1555]. They are thought of as congenital and considered certain, probable, or possible (see Chap. 2). In the first year of life, brain tumors become more frequent (7.7%) [1555], and their oncotype composition also changes. The most frequent are astrocytomas, followed by medulloblastomas, ependymomas, and plexus papillomas [2714, 1209]. Supratentorial locations and neuroepithelial tumors (89%) also prevail. Cerebellar astrocytomas are less frequent than in infancy. The hemispheric astrocytomas are mostly benign, glioblastoma being almost unknown, with the exception of some series [2922]. Metastases are rare and generally limited to the adrenal carcinoma.

The incidence of oncotypes in relation to site is different from that in adults. While in the adult there is a clear predilection for the anterior rather than posterior parts of the brain, especially for gliomas [2903], in infancy the predilection tends to be reversed, with 50% of tumors in the posterior fossa, more or less equally subdivided into medulloblastomas and astrocytomas. Only 12%–25% of tumors, mostly gliomas and ependymomas, develop in the cerebral hemispheres. Astrocytomas are generally the most common oncotype: the incidence in Connecticut is 0.81/100 000 [746]. Meningiomas, oligodendrogliomas, and pituitary adenomas are rare.

In a Japanese series [2945], brain tumors globally represent 14.9% of all tumors. Gliomas represent 60.6%, followed by craniopharyngiomas with 12.5%, other congenital tumors with 5% and pineal region tumors with 8.5%. Among neuroepithelial tumors, astrocytomas are the most frequent (27.3%), followed by ependymomas (14.8%). While tumors such as astrocytoma and ependymoma are clearly more frequent in infancy, others such as glioblastoma and anaplastic astrocytoma are less frequent.

It is important to remember that tumors in infancy have a wide range of features, depending on different factors: The ability of fetal cells to differentiate; the effects of anaplasia, which may appear later as an expression of tumor progression; the possibility of aberrant or heteroplastic differentiation, especially in embryonal tumors; the fact that the neoplastic differentiation has wider limits than normal [2876].

### 8.2.3

#### Sex

The incidence of intracranial tumors is slightly higher in males than in females: 8.5 and 7.9/100 000, respectively, in the United States [3593]. Gliomas clearly prevail in males, while meningiomas and pituitary adenomas are more common in females. For example, in the Manitoba Canadian study [3344] the incidence data were as follows: 4.2 versus 2.7 for malignant gliomas, 1.3 versus 0.8 for differentiated gliomas, 1.5 versus 3.1 for meningiomas, and 1.4 versus 2.1 for pituitary adenomas.

### 8.2.4

#### Race

The incidence of all intracranial tumors and of individual oncotypes is higher in whites than in blacks [864, 2685, 1772, 384, 3535]. All types of glioma are more frequent in whites. Data obtained from the Georgia Tumor Registry (USA) showed a white to black ratio of 2.3:1 [2216]. The maximum difference in frequency appears to occur for oligodendrogliomas. The relative frequency of the oncotypes is different: In black people, gliomas are less frequent, but meningiomas and pituitary adenomas are relatively more frequent. In infantile tumors, the male to female ratio is different for medulloblastomas [384].

## 8.3

### Epidemiology of Intraspinal Tumors

Data regarding the epidemiology of spinal tumors are relatively scarce. They are less frequent than intracranial ones with a ratio varying between 9:1 and 15:1 [2954]. The incidence of spinal tumors varies from 0.9 [1910] to 2.5/100 000 [1823], with more frequent values between 1.2 and 1.3 [531, 2609, 49, 2954, 921]. The distribution of the histological types in broadly different population studies such as in Iceland [1184], Israel [1910], and Rochester [2954] is similar: neurinomas and neurofibromas (26%–38%), meningiomas (13%–28%), and gliomas (11%–13%) encompassing astrocytomas and ependymomas. In infancy, spinal tumors are less frequent than in the adult (11% vs. 20.8%) [49]. The composition of oncotypes is also different; meningiomas and neurinomas are rare, and the congenital and sarcomatous tumors are more frequent.

## Astrocytic Tumors

### 9.1

#### Nosological Problems

Astrocytic tumors were originally subdivided into fibrillary and protoplasmic types [133, 134]. The gigantocellular and pseudopapillary types, identifiable with astroblastoma, were subsequently added [2861], so that five varieties were definitely recognized [3799]: fibrillary, protoplasmic, gigantocellular, astroblastoma, and the malignant variant. Still stemming from the original classification [133, 134], another nomenclature was used for these tumors, with the introduction of the pilocytic and gemistocytic varieties [2602, 823]. The term pilocytic derives from the Greek word for “hair” and indicates the elongated and bipolar aspect of the cells. The term gemistocytic refers to cells which in the German nomenclature were described as *gemästete Zellen* from the Greek word γεμίζω for “to stuff.” On the basis of this subdivision and with the introduction of the concept of anaplasia, expressed by the “grading” system [1661], astrocytomas were subdivided into protoplasmic, fibrillary, pilocytic, gemistocytic, and anaplastic [2899, 2903].

Pilocytic astrocytomas are characterized by elongated and bipolar elements and are subdivided into “adult” and “juvenile” types according to their firm or loose texture. This scheme differs from that of Zülch as in the latter, astrocytomas with a pilocytic aspect are included in the fibrillary variant when they are situated in the cerebral hemispheres and in the spongioblastoma group when they are paraventricular or cerebellar. Zülch [3799] conceived of the spongioblastoma group as an all-encompassing one to which most of the midline gliomas belong, i.e., the spongioblastoma of the chiasm, hypothalamus, brainstem and aqueduct, cerebellum, fourth ventricle, and some of the “Stiftgliome” of the spinal cord. They have a common origin from the subependymal glia and share the presence of Rosenthal’s fibers, which are characteristic of subependymal glia in neoplastic, degenerative, and inflammatory processes. Earlier studies of anatomical systematics and cytoarchitectonics have interpreted spongioblastomas as typical tumors of the dorso-lateral prechordal sheet. Their main location is, therefore, the neural tube equally in its dorsal and basal part, spinal cord, medulla oblongata, pons, quadrigeminal plate, cerebellum, thalamus, hypothalamus, chiasm, and optic nerve. Typical subependymal spongioblastomas are then found at different points of the ventricular wall and could originate from the allocortex, hence from the olfactory cortex, cingulate gyrus, hippocampus, indusium griseum, corpus callosum, splenium, and fornix.

The endless debate started when the term spongioblastoma, which indicated a malignant glial tumor, was replaced by glioblastoma [133]. The former remained to

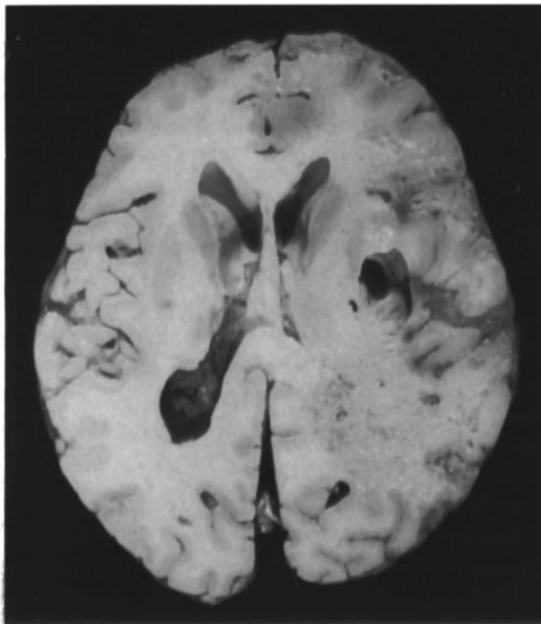


Fig. 9.1. Hemispheric cystic astrocytoma

indicate a group of benign tumors characterized by elongated cells resembling the spongioblasts of cytogenesis [2861, 1393] and mainly located in the region of the optic nerve, chiasm, and hypothalamus. These tumors were called spongioblastomas by some [3799] and piloid [823] and pilocytic astrocytomas [2899] by others. The latter authors reserved the term “spongioblastoma” to designate a rare tumor with malignant behavior whose cells resembled the primitive spongioblasts of cytogenesis (see Chap. 15).

The recent classification by WHO [1702] subdivides astrocytic tumors as follows:

1. Astrocytoma
  - Fibrillary
  - Protoplasmic
  - Gemistocytic
  - Mixed
2. Anaplastic (malignant) astrocytoma
3. Glioblastoma
  - Giant cell glioblastoma
  - Gliosarcoma
4. Pilocytic astrocytoma
5. Pleomorphic xanthoastrocytoma
6. Subependymal giant cell astrocytoma (usually in association with tuberous sclerosis)

In the present book, astrocytomas are described on the basis of their histological features and location. Fibrillary, protoplasmic, gemistocytic, pilocytic, and ana-

plastic variants of astrocytoma will be considered. Very often, however, a clearcut distinction between them is difficult, especially between the fibrillary and the protoplasmic variants.

## 9.2

### Astrocytic Tumors of the Cerebral Hemispheres

#### 9.2.1

##### Astrocytomas

##### 9.2.1.1

###### *Frequency, Age, Site and Clinical Features*

Astrocytomas appear especially in the third and fourth decades of life and are in the main frontal, parietal, and temporal. They represent 25%–30% of all hemispheric gliomas. In our series, they represent 24.5% of gliomas and 11.3% of all intracranial tumors.

Clinical symptomatology depends on the location of the tumor. Site-specific signs prevail over those of increased intracranial pressure. The most common presenting symptom is an epileptic seizure, which occurs in more than half of the patients. For the clinical diagnosis, it is of paramount importance to remember that site-specific symptoms and epileptic seizures may occur for many years prior to recognition of the tumor.

##### 9.2.1.2

###### *Macroscopic Appearance and Imaging*

The tumor is firm, grayish-white, and difficult to distinguish from the surrounding tissue. Usually solid, it can occasionally include cysts of various dimensions. It is found in the white matter (Fig. 9.1).

The tumor is usually discovered by computed tomography (CT) scan and magnetic resonance imaging (MRI), but it may happen that a tumor shows a normal CT scan. Typically, the tumor appears as a hypodense, non-enhancing lesion, with a mass effect (Fig. 9. 2a). The enhancement does not exclude the diagnosis of astrocytoma; however, it usually indicates a poorer prognosis. On MRI, the lesion has low intensity on T1-weighted images and increased intensity on T2-weighted images. The distinction between tumor and peritumoral edema is very difficult (Fig. 9.2b). Positron emission tomography (PET) scan may be useful because the tumor is hypometabolic.

##### 9.2.1.3

###### *Microscopic Appearance*

*Fibrillary Variant.* The tumor is composed of astrocytic elements with delicate processes, well demonstrated especially with silver impregnation methods, phospho-

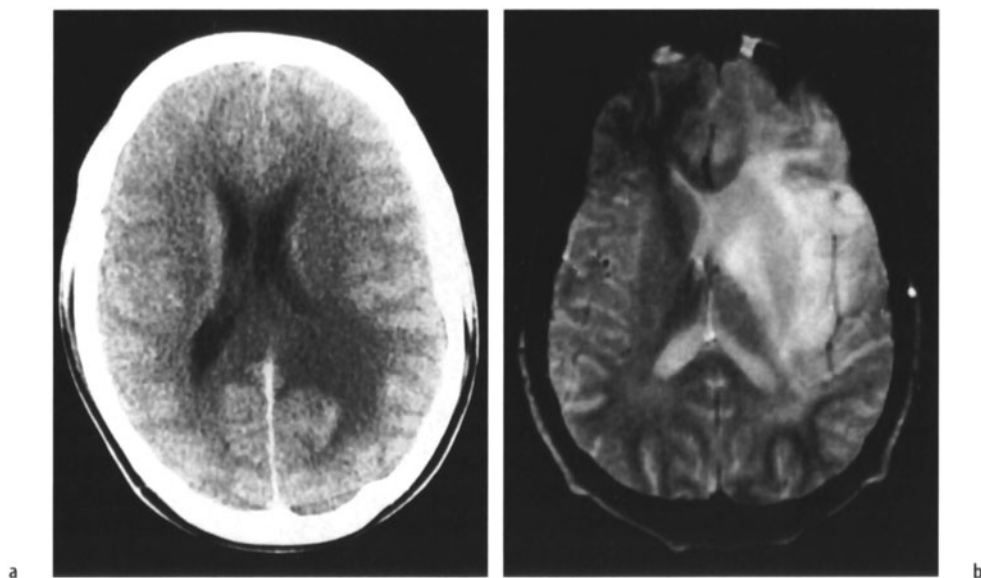


Fig. 9.2a,b. Fibrillary astrocytoma on a computed tomography (CT) and b magnetic resonance imaging (MRI)

tungstic acid–hematoxylin (PTAH), and glial fibrillary acidic protein (GFAP) (Fig. 9.3). The nuclei are round or oval, isomorphous, but sometimes of variable size and chromatin content so as to appear polymorphic, especially in the peripheral zones. Mitoses are rare. The cell density is low but most often higher than that of the white matter; sometimes it is quite difficult to recognize the tumor edge even microscopically. The cells are regularly distributed, but in some cases they are arranged in particular patterns such as the “stepladder” one; alternatively, they may infiltrate the cortex, forming perineuronal satellitosis.

The most important regressive event is represented by fluidification with microcyst formation. Calcifications are found in 15% of cases [2994].

Blood vessels are scarce and of small caliber and no evidence of either neovascularization or endothelial hyperplasia is present.

The differential diagnosis includes normal tissue, reactive gliosis, anaplastic astrocytoma, and oligodendroglioma. The tumor is usually distinguishable from reactive gliosis, because in the latter astrocytes are scarcer and more regularly distributed and feature larger processes more intensely positive for GFAP. General criteria are available for the distinction between tumoral and reactive astrocytes [781], but they cannot be considered as absolute. For example, the occurrence of mitoses is inconclusive because they can be found in reactive astrocytes as well [3023]. The criteria for the distinction between fibrillary and anaplastic astrocytoma will be set forth later. Fibrillary astrocytoma is distinguished from oligodendroglioma by the presence of a fibrillary background, the aspect of the nuclei, the absence of the cytoplasmic “halo” around the nucleus, the type and distribution of blood vessels, and the lower frequency of calcifications.

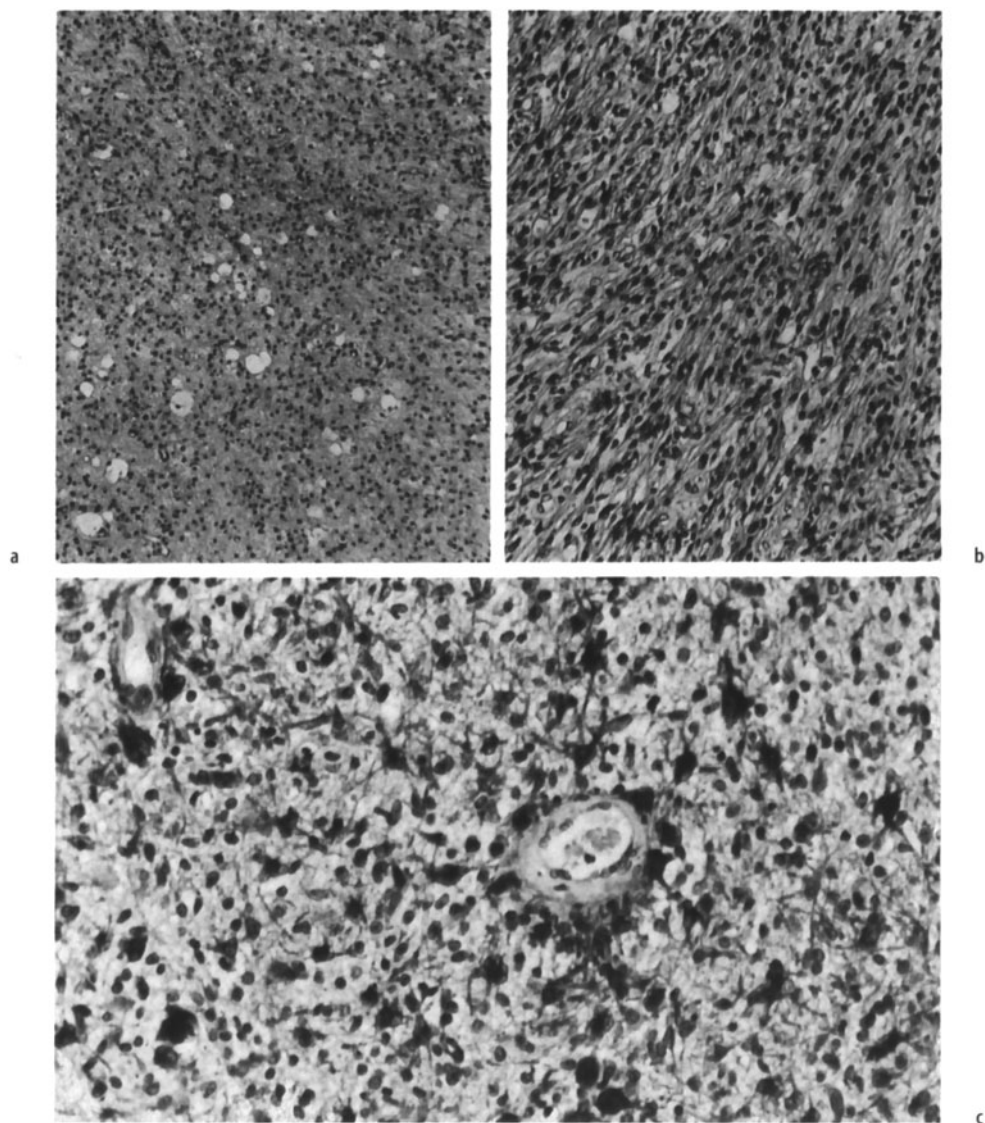


Fig. 9.3a–c. Fibrillary astrocytoma, various aspects. H&E, a  $\times 200$ , b  $\times 300$ . c Glial fibrillary acidic protein (GFAP)-positive reaction in many processes. PAP-DAB,  $\times 400$ . (From [3027])

*Protoplasmic Variant.* The protoplasmic variant is mostly found in the cortex and originates from astrocytes of the central cortical layers. The tumor has ill-defined borders (Fig. 9.4) and a homogeneous aspect, is grayish-white or pinkish, and often contains small or large cysts. The cells show eosinophilic and GFAP-positive cytoplasm with short processes and round or oval nuclei (Fig. 9.5a). Typically, numerous microcysts, which may be confluent, occur (Fig. 9.5b). Only rarely is the histological picture pure, and both protoplasmic and fibrillary astrocytes are often present.



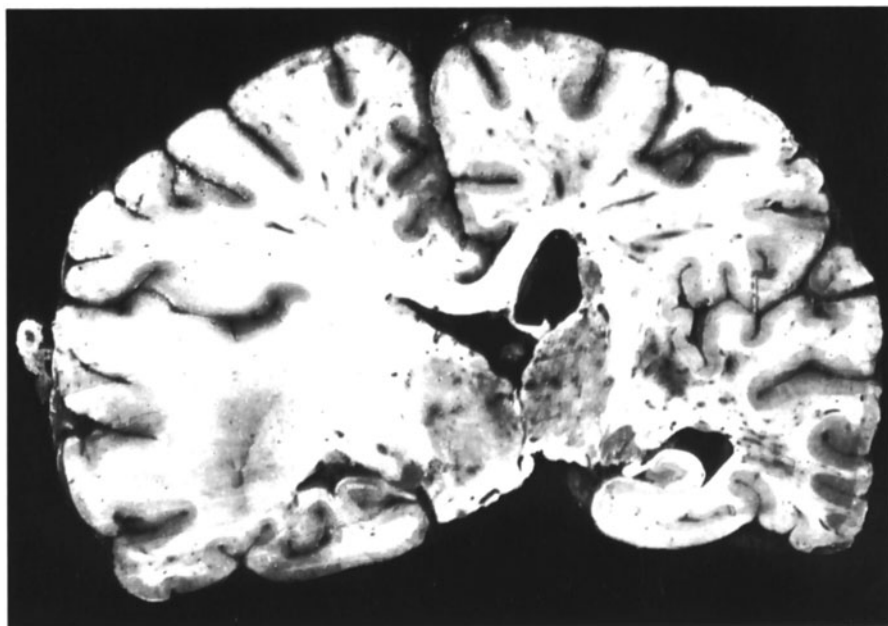


Fig. 9.4. Temporoparietal protoplasmatic astrocytoma with ill-defined borders

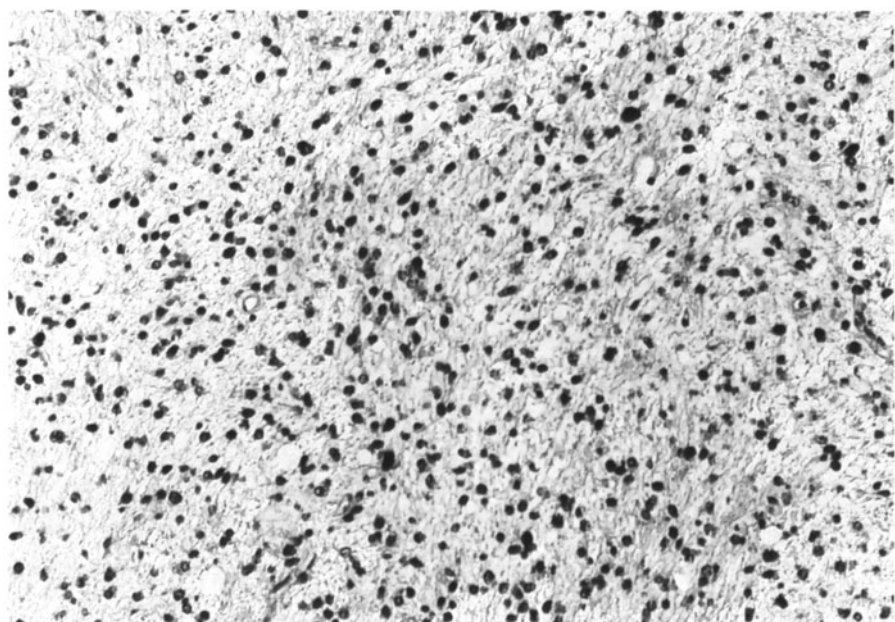
*Gemistocytic Variant.* The gemistocytic variant is characterized by large cells with expanded and eosinophilic cytoplasm provided with numerous, very short processes (Fig. 9.6a), variably GFAP positive (Fig. 9.6b). The nucleus is dark and peripherally situated. The gemistocytic appearance rarely involves the whole tumor; often it occurs focally in otherwise fibrillary or protoplasmic astrocytomas. Perivascular lymphoplasmacellular infiltrates are more common than in other types of astrocytoma (Fig. 9.7a). Macrophages and CD8<sup>+</sup> lymphocytes have been found in some astrocytomas [2851].

#### 9.2.1.4

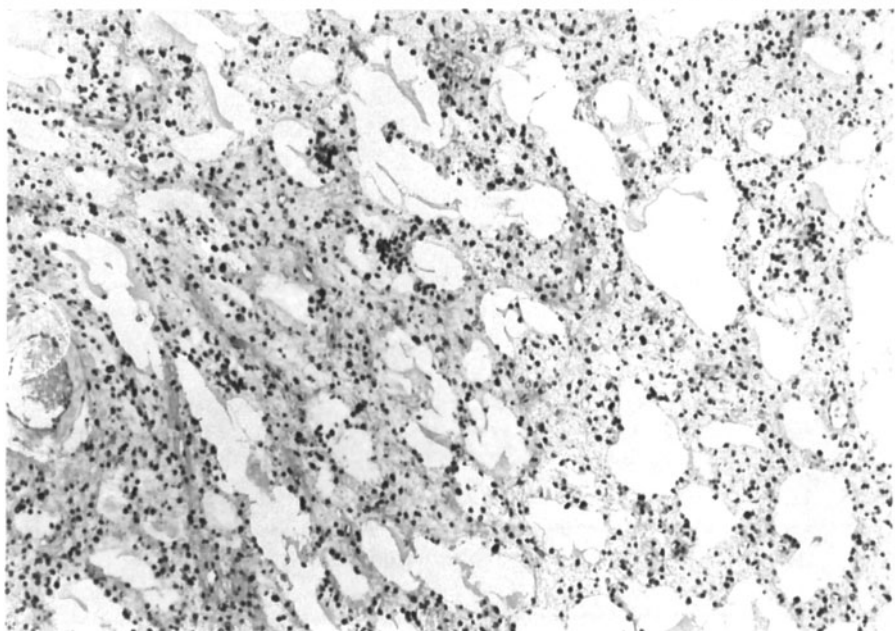
##### *Pilocytic Astrocytoma*

Lobar pilocytic astrocytoma is not frequent, but is now well recognized; the tumor is fairly circumscribed and frequently cystic. Although it is more frequent in children and young adolescents [1021], it may also occur in adults [17]. It is not easy to recognize, especially in small biopsies. Clinically, the tumors are frequently associated with epileptic seizures. Their radiological imaging is very important; in contrast to fibrillary astrocytomas, which are hypodense on CT and hypointense on MRI, they may show contrast enhancement similar to that of malignant gliomas. This may raise serious problems in differential diagnosis.

The tumor is composed of elongated, bipolar cells with long wavy processes often organized in parallel bundles, which take characteristic shapes on longitudinal or

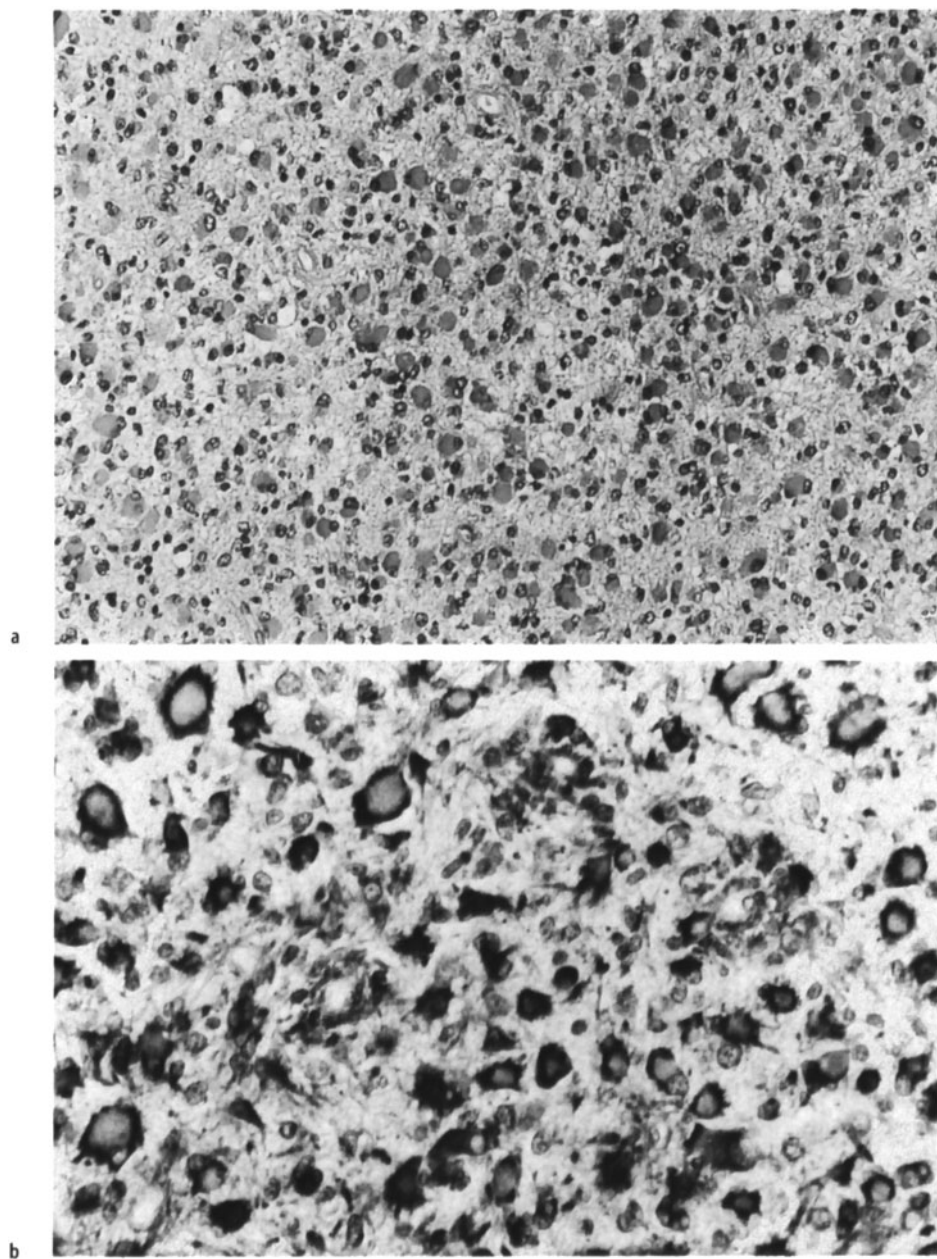


a

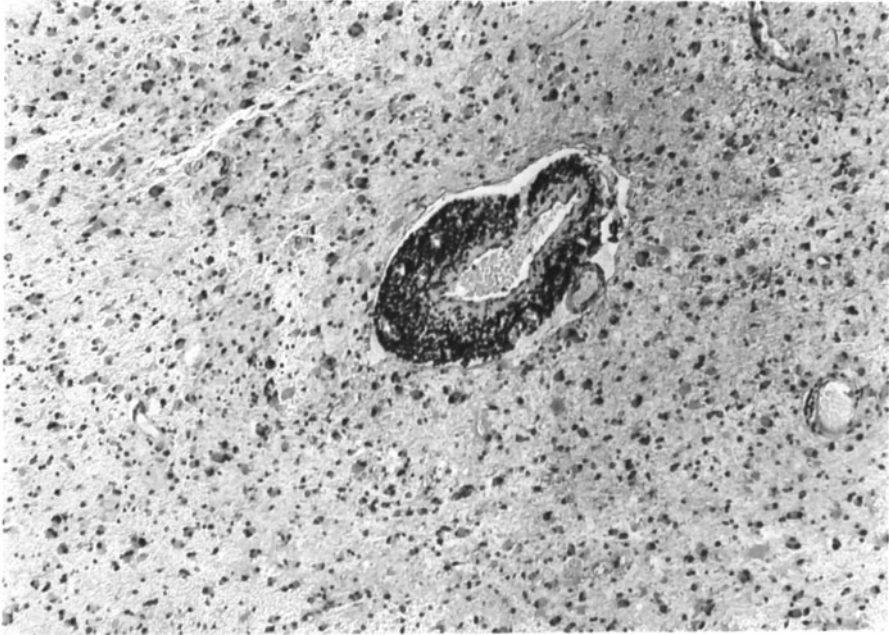


b

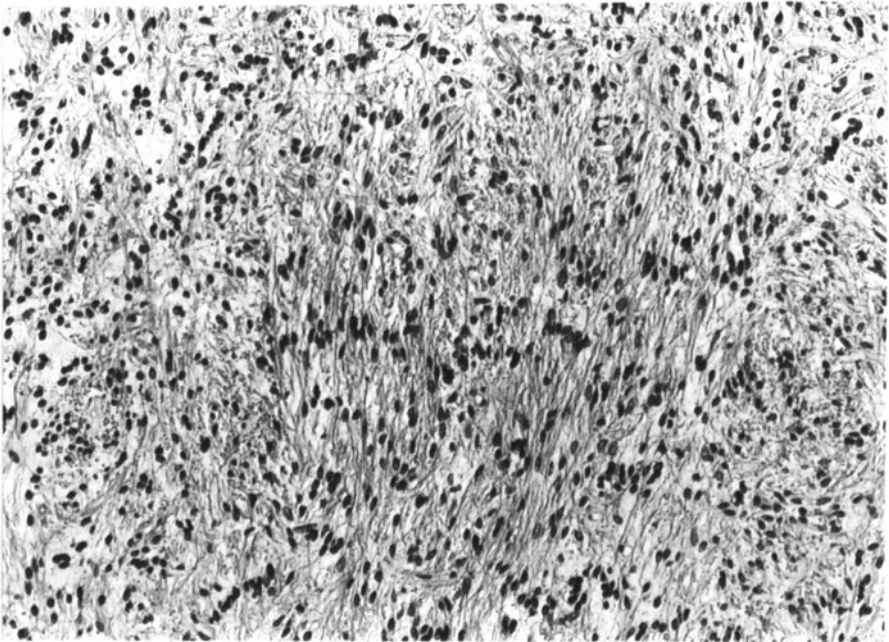
**Fig. 9.5a,b.** Protoplasmic astrocytoma. **a** Low cell density, round nuclei, and short processes. H&E,  $\times 300$ . **b** Formation of microcysts. H&E,  $\times 150$



**Fig. 9.6a,b.** Gemistocytic astrocytoma. **a** Expanded cytoplasm. H&E,  $\times 300$ . **b** Glial fibrillary acidic protein (GFAP)-positive cytoplasm. PAP-DAB,  $\times 400$ . (From [3024])



a



b

**Fig. 9.7. a** Gemistocytic astrocytoma; perivascular lymphocytic infiltrate. **b** Pilocytic astrocytoma; elongated, bipolar cells are organized in bundles. H&E,  $\times 200$



Fig. 9.8. Double immunogold staining for glial fibrillary acidic protein (GFAP) (*small granules*) and vimentin (*large granules*) in an astrocytoma,  $\times 50\,000$

transverse section (Fig. 9.7b). The same applies to the nuclei which can, therefore, show an oval or a round shape.

They alternate with stellate cells characterized by a sparsely fibrillary cytoarchitecture. GFAP is intensely positive in the long processes and less constant in stellate cells, whereas vimentin is strongly positive. As in all types of astrocytoma, intermediate filaments can be seen under the electron microscope and marked by immunogold procedures with GFAP and Vimentin antibodies. The two antigens colocalize (Fig. 9.8). Multinucleated cells may be present. Very characteristic is endothelial hyperplasia with glomeruloid formations, which do not indicate malignant transformation. Rosenthal's fibers and often calcifications are present.

From time to time, mostly in the neurosurgical literature, series of cases usually with the characteristic histological features described above and generally associated with long survival are reported [3044, 526, 2544].

There are several peculiar features, e.g., a protoplasmic-like appearance, for which the denomination "piloprotoplasmic astrocytoma" has been proposed [1608].

"Eosinophilic granular bodies" may occur. They are positive to  $\alpha_1$ -antichymotrypsin,  $\alpha_1$ -antitrypsin, ubiquitin, and  $\beta$ -amyloid precursor protein. They are, therefore, proteinaceous bodies that undergo ubiquitin degradation [1609]. Round, granulated bodies and eosinophilic hyaline GFAP-positive droplets occur, representing degenerative changes [1341].

The tumors are usually benign, but an anaplastic transformation is possible, albeit rare. The tumor may extend into the leptomeninges and show distant seeding with a preserved benign character.

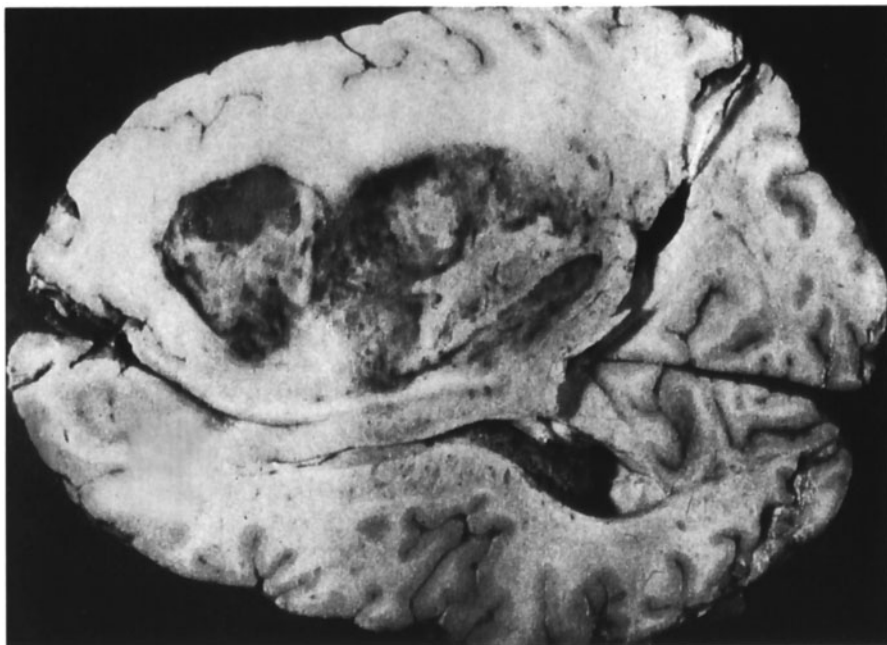


Fig. 9.9. Hemispheric anaplastic astrocytoma

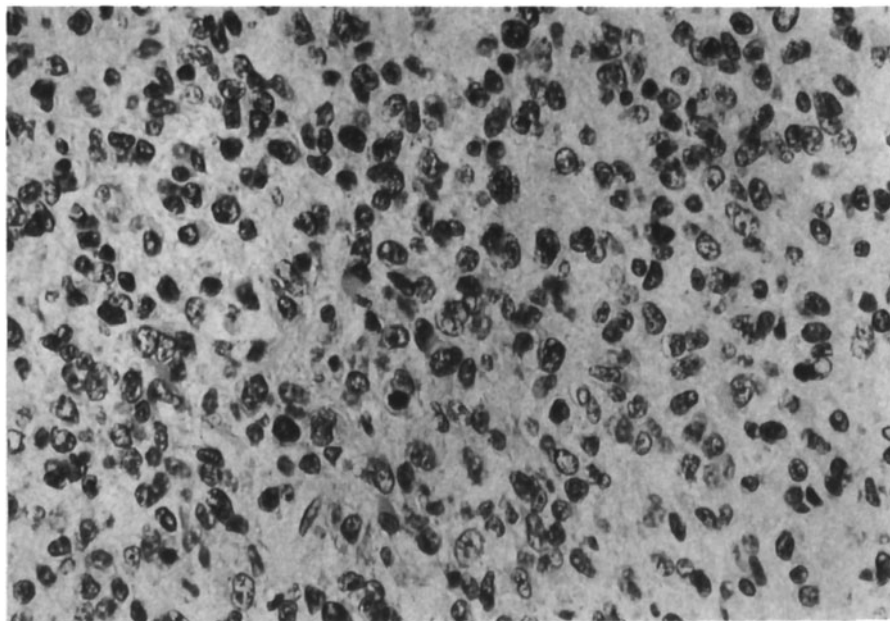
A problem of great interest has been that of the origin of the tumor; the biphasic aspect suggests that it originates from distinct glia cell populations, i.e., radial glia or 0.2A cells persisting in the young patients [2705, 3516].

#### 9.2.1.5

##### *Anaplastic Variant*

This neoplastic histotype represents the anaplastic transformation of an astrocytoma without reaching the extreme degrees of anaplasia seen in the glioblastoma, which are represented mainly by large areas of necrosis and prominent vascular disarrays. Since it represents the transformation of an astrocytoma, it often shares macroscopic characteristics and location of the latter. It usually appears in slightly older patients than the other variants. The macroscopic aspect is intermediate between those of astrocytoma and glioblastoma (Fig. 9.9).

The histological characteristics of anaplasia may be present diffusely within the tumor or be circumscribed and focal. They are represented by greater cellular density and nuclear polymorphism, more frequent mitoses, and less evident astrocytic features (Fig. 9.10). The pattern of GFAP production is characteristic: As the extent of anaplasia increases, more and more GFAP-negative cells and mitoses appear, consistently with the concept that anaplasia depends on the genotypic and phenotypic tumor heterogeneity (see Fig. 7.2).

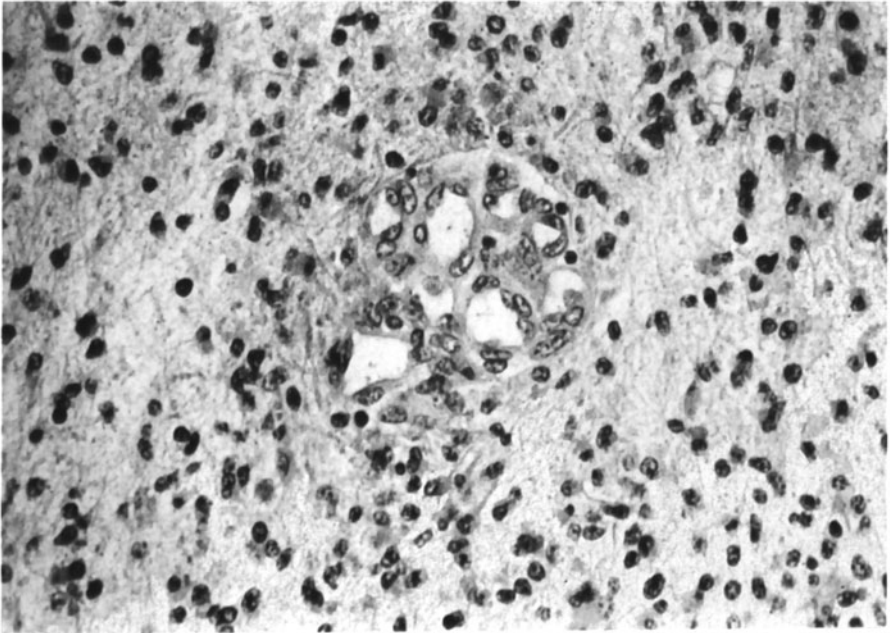


**Fig. 9.10.** Anaplastic astrocytoma. Increased cell density, less evident astrocytic features, and more frequent mitoses. H&E,  $\times 400$

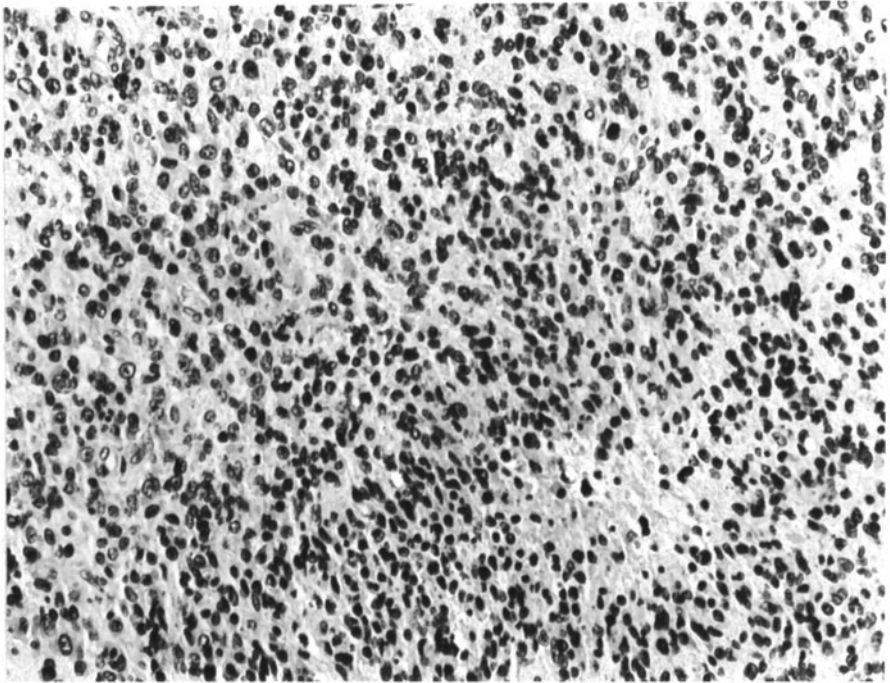
Compared with other astrocytomas, this tumor is more infiltrating and shows a greater tendency to invade the cortex and the subpial region. It is a matter of debate whether stromal changes, such as an increase in blood vessels and early endothelial hyperplasia (Fig. 9.11a), as well as the occurrence of few, small, circumscribed necroses (Fig. 9.11b), still indicate an anaplastic astrocytoma or already the picture of glioblastoma. This is extremely important from the practical point of view, when the recognition of the variant has to be made on small biopsy samples. In the opinion of many authors, only large and extensive necroses with pronounced vessel changes are indicative of glioblastoma. In our experience [3026], early endothelial hyperplasia and isolated small necroses are still compatible with the diagnosis of anaplastic astrocytoma.

Since anaplasia can be a focal event and because of the extreme heterogeneity of malignant gliomas, incomplete sampling at surgery may account for the diagnosis of astrocytoma instead of anaplastic astrocytoma and of anaplastic astrocytoma instead of glioblastoma. The diagnosis of anaplastic astrocytoma on surgical material is more frequently made than in autopsy material. Since anaplasia is an evolving phenomenon, it could be that a tumor appearing originally as an anaplastic astrocytoma becomes transformed into a glioblastoma in time [3011]. As the two oncotypes have different survival rates they must be kept distinct, and the differential diagnosis has to be made.





a



b

**Fig. 9.11a,b.** Anaplastic astrocytoma. **a** Early endothelial hyperplasia. H&E,  $\times 300$ . **b** Small circumscribed necrosis. H&E,  $\times 200$



### 9.2.1.6

#### *Prognosis and Treatment of Hemispheric Astrocytomas*

The hemispheric astrocytoma has an extremely variable clinical course due to the potential appearance of malignant transformation. Survival varies from 5 to 15 years down to figures which are very close to that for glioblastoma. The well-differentiated astrocytoma may undergo anaplastic changes, as is well known, but the time when these appear is not predictable, even though the general opinion is that they do not arise for a long time after diagnosis. It is then necessary to identify histological prognostic factors. The possibility of malignant transformation over time, however, renders the prognosis of well-differentiated astrocytomas constantly sub judice. This influences the therapeutic strategy.

The most important problem is that of recognizing the malignant transformation. First of all, there may be a surgical sampling error, because of the focal appearance of anaplasia, especially when the diagnosis is made on very small specimens. Secondly, some histological or cytological signs may be differently interpreted from the prognostic point of view: For example, nuclear polymorphism may be overestimated. The histological heterogeneity of gliomas has been found to be high [2578]. For this reason, the greater the amount of tissue examined, the more reliable the diagnosis.

Whilst no significant prognostic differences between fibrillary and protoplasmic astrocytomas have been observed, it is known that the gemistocytic variety bears a shorter survival rate due to the more frequent coexistence of signs of anaplasia [2903, 3026]. It has been observed that the presence of more than 60% gemistocytes in a fibrillary astrocytoma has the same poor prognostic significance as anaplastic astrocytoma [1787]. The study of the prognostic significance of individual histological factors in astrocytomas demonstrated that cell density (low or medium), nuclear polymorphism (absent or moderate), number of blood vessels, lymphoplasmacellular perivascular infiltrates, and presence of a limited number of mitoses (less than five per ten high-power fields, HPF) do not seem to influence survival [3026]. A low mitotic count was already recognized as not excluding the possibility of long survival [822]. In contrast, a correlation with shorter survival has been found for cases containing blood vessels of variable caliber [3026]. This variability, however, could be indicative of "sampling error," i.e., of the existence of anaplastic areas in parts of the tumor which were not removed.

Utilizing the labeling index (LI) obtained with bromodeoxyuridine (BrdU), it has been observed that the 3-year survival is significantly greater for cases with a LI below 1% [1412]. A positive correlation has also been found between the BrdU LI and the recurrence-free interval [981]. The macroscopic presence of cysts seems to be related to a better prognosis [1110, 822, 2004].

Clinical factors correlated with longer survival are young age, long duration of preoperative symptoms, epileptic fits at onset, absence of important pre- and, especially, postoperative neurological signs [3634, 1886, 2637, 3530]. The uptake of contrast material on preoperative CT scanning would seem to be a prognostically independent factor: The astrocytomas which take up the contrast medium have a worse prognosis [2637]. In some of these cases, it could be a sampling error in an anaplastic astrocytoma.

A total of 30%–65% of patients with well-differentiated astrocytomas are alive at 5 years, and 20%–48% at 10 years.

Patients surviving for between 10 and 30 years are on record [660, 3631, 1152, 2207, 3093, 1022], even in the absence of any therapy [822]. In a series of 461 patients the 15-year survival was 15% [3151].

As has been said, the duration of survival can be abruptly shortened by malignant transformation. The frequency of this event is not exactly known; however, except for a few cases [2004, 2637], the percentage of astrocytomas showing signs of anaplasia at reoperation for recurrence or at autopsy is high in the many series reported and varies from 49% to 85% [2123, 1886, 3251, 3541]. The risk of malignant transformation seems to be greater in the first years after surgery [3251]. From the clinical standpoint, it would be very important to be able to detect the tumor areas which are undergoing anaplastic transformation; the results which are being acquired with fluorodeoxyglucose PET (FDG-PET) seem encouraging [940].

Anaplastic astrocytoma has a worse prognosis than the well-differentiated one. The recognition of anaplasia is theoretically very easy, but practically it is still a controversial issue. In our experience, a mitosis count  $>5$  per ten HPF, cell density greater than 800 nuclei/HPF, and endothelial hyperplasia are the fundamental elements for its identification in the group of astrocytomas. A standardized evaluation of nuclear atypia, necrosis, mitoses, and endothelial proliferations leads to a good correspondence with survival [655, 1676]. Once anaplasia is established, circumscribed or diffused, parenchymal only or also stromal, it cannot be further graded if evaluated in multivariate analysis [3026] (Fig. 9.12). The prognostic importance of single histological factors in anaplastic astrocytomas has been highlighted by some studies [394, 995, 3250]. Whilst endothelial proliferation is constantly associated with a worse prognosis, cellular density, nuclear polymorphism, number of mitoses, and perivascular lymphoplasmacellular infiltrates seem to be of poorer prognostic significance [3250]. Others [995] have noted that a high number of mitoses entails a shortening of survival. Analysis of the DNA pattern added to that of other histological features could perhaps contribute to identifying cases with a more aggressive behavior [563].

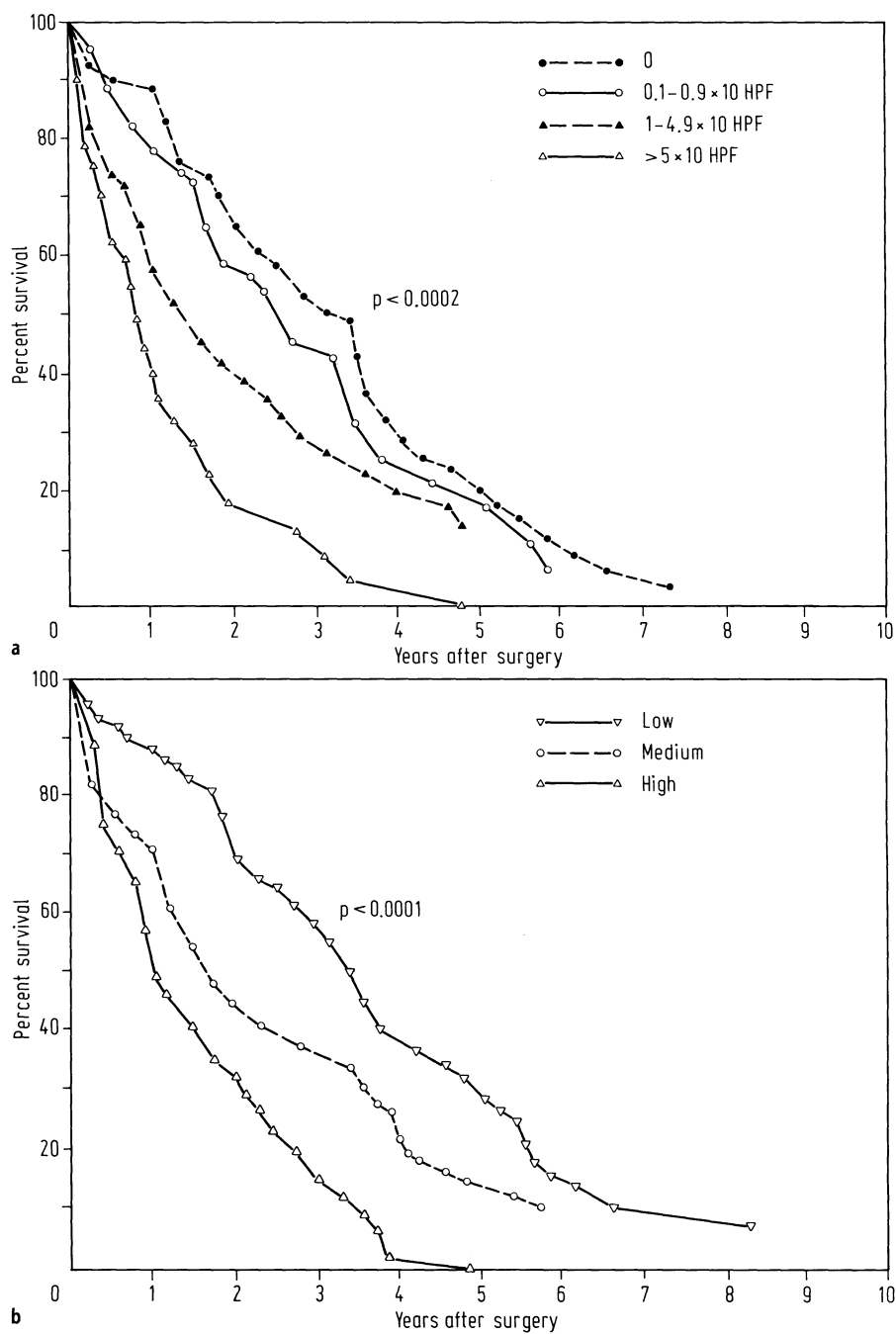
Young age and a high performance status of the patients are clinical factors unanimously recognized as entailing a better prognosis. A complete response instead of a partial one as judged by CT scan after radiochemotherapy is predictive of longer survival [2359].

Surgery is the first and basic diagnostic and therapeutic approach in astrocytomas [1940, 1110, 3634, 1886, 3251]. There is little doubt about the surgical treatment of large and symptomatic astrocytomas.

A significant correlation has been found between survival and extension of surgical removal with a 50%–60% survival rate at 5 years after macroscopically total removal [1886, 2637, 3251, 2304, 202]. All these studies are limited, however, by their retrospective nature, and prospective studies are not yet available.

A possible rationale for removing as much tumor as possible could be given by kinetics data [1402], which suggest that well-differentiated astrocytomas are mainly composed of cells which are not in cycle, and that passage from the “nonproliferating” to the “proliferating” pool is very limited.

Another point in favor of surgery is the necessity to ascertain the histological diagnosis and to discover signs of malignancy indicating adjuvant therapies.



**Fig. 9.12a–d.** Hemispheric astrocytoma. Survival by **a** number of mitoses per ten high-power fields (HPF), **b** cell density. **c,d** see p. 153

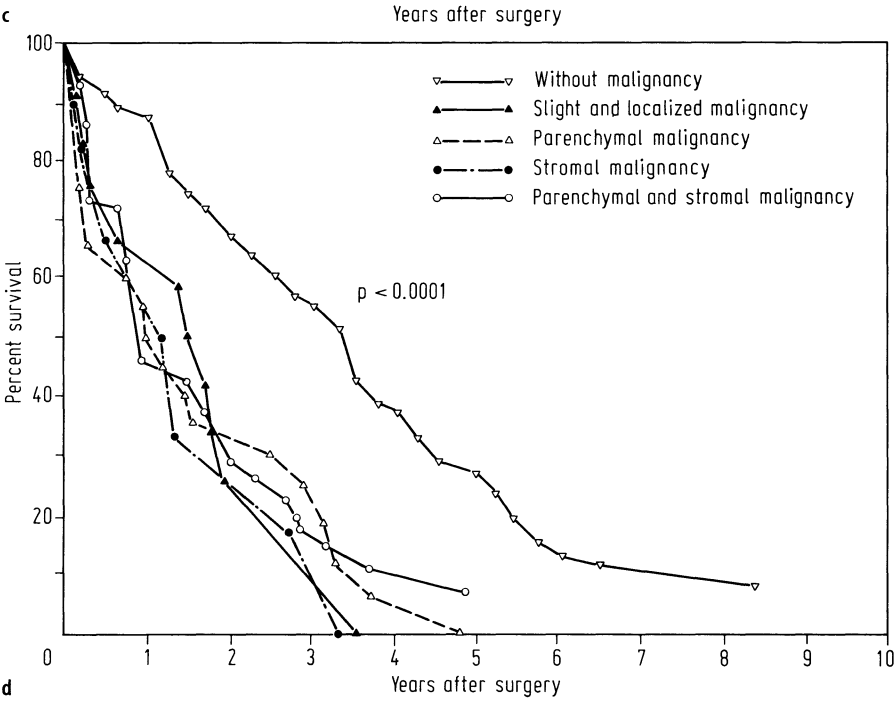
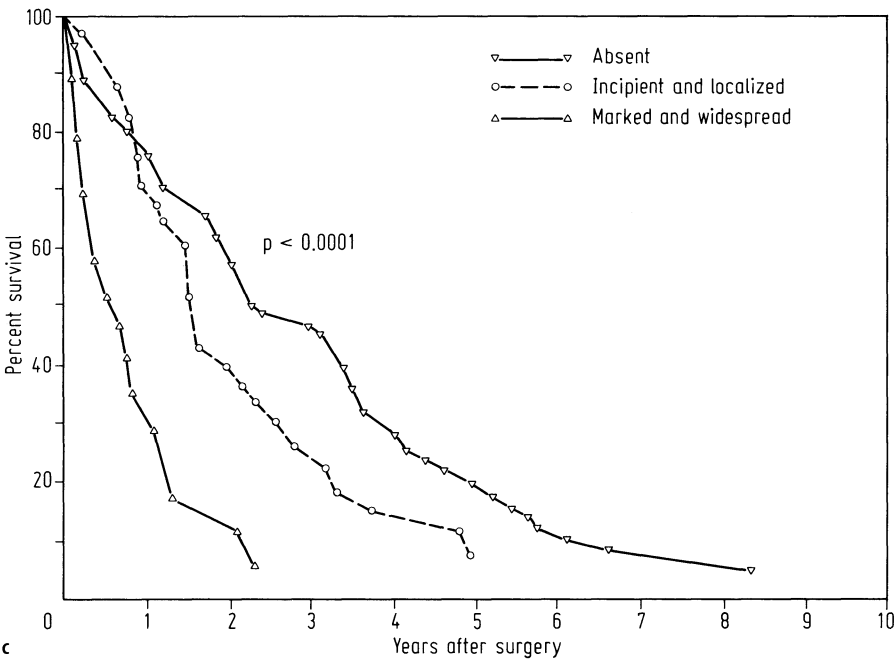


Fig. 9.12. c Endothelial hyperplasia and d different patterns of malignancy

It must be stressed that 30% of anaplastic astrocytomas are hypodense on a CT scan [476], and often the histological signs of anaplasia are minimal and localized [3026]; the risk is that they may go undiscovered in a simple biopsy.

When hypodense tumors cannot be approached by surgery either because of their location (basal ganglia, thalamus-hypothalamus, pineal region, brain stem) or their small dimensions, the histological diagnosis may be made on stereotactic biopsy material. The diagnosis of oncotype can be obtained in 80% of cases, provided that specimens are taken by multiple tracks, permitting tumor mapping [80, 2515]. It is more difficult to recognize the malignancy grade. This procedure has also been proposed for the removal of the tumor itself, with encouraging results, provided that it is circumscribed and of small dimensions [1627].

When one is dealing with young adult patients with a negative neurological examination, a clinical history of epileptic seizures, and a small hypodense lesion without enhancement after injecting contrast medium, the choice of treatment is controversial. Often, they are well-differentiated astrocytomas, slowly growing, which may have a very long survival even without any therapy. In many cases, conservative treatment with anti-epileptic drugs is adopted, keeping more aggressive approaches in case of clinical worsening [412]. From their kinetic and biological characteristics, there is no neuroradiobiological rationale for the external radiotherapy of differentiated astrocytomas, save sterilizing possible anaplastic foci in the remaining portions [3019] or delaying or diminishing the incidence of malignant transformation [2304].

There is no unquestionable demonstration of the efficacy of postoperative radiotherapy. The only available data on the usefulness of irradiating well-differentiated astrocytomas come from retrospective studies [1595]. The survival of patients biopsied or treated surgically by partial removal is improved by radiotherapy [1907, 2304, 3667, 2457, 2206], especially with high doses (53–55 Gy) to the tumor volume [3153], whereas radiotherapy does not seem to improve survival after total removal [2637]. In cases with extensive removal, if postoperative radiotherapy is not performed, a follow-up with CT and MRI must be done, and according to the result, reoperation and/or irradiation carried out. The controversy concerning whether to irradiate well-differentiated hemispheric astrocytomas or not will remain until ongoing prospective studies take into account the role of the various approaches [3151, 1596].

The therapeutic efficacy of interstitial irradiation with  $^{192}\text{Ir}$  and  $^{125}\text{I}$  is well documented as an alternative to surgical removal for lesions less than 3 cm in diameter or located in highly functional areas [3361, 212, 2358, 2516, 1778]. Its neuroradiobiological rationale is unopposable: the administration of a high radiation dose, specifically cytotoxic for tumor cells, without damaging the adjacent normal nervous tissue. The same rationale is exploited by recent procedures of radiosurgery, whose results are under evaluation [554].

The prognosis of pilocytic hemispheric astrocytomas is relatively good. Recently, 30 patients with the cystic paraventricular form have been described, with an average age of 22 years. The tumors were characterized by Rosenthal's fibers, microcysts, and calcifications. A mean survival of 6.95 years for males and 5.17 years for females was observed, but many patients were still alive at the time of the last follow up [526]. In another series of 51 patients, with a mean age of 18 years, the tumors were mainly

cystic, temporoparietal, with a mean survival of 17 years [2544]. Following complete or incomplete excision, 80% or more survive 10 years [1021, 3151]. If pilocytic astrocytoma is totally removed, the patient usually should not be irradiated.

In anaplastic astrocytomas, macroscopically total surgical removal leads to a lower morbidity and longer survival than incomplete resections.

In patients with anaplastic astrocytomas receiving postoperative radiotherapy, surgical removal leads to better survival as compared with biopsy alone [2401], but the importance of the extent of removal, whether total or partial, is still unclear [2412]. Postoperative radiotherapy improves the prognosis significantly compared with surgical removal alone [1022, 3250]. Reoperation for recurrence may be useful, but only in selected cases [60, 1248]. The median survival after surgery plus high dose radiotherapy (which gives the best results) of patients with anaplastic astrocytomas (with or without chemotherapy) is around 28 months [2402], with 62% at 18 months [2402], 38%–50% at 24 months, and 18%–20% at 5 years [1907].

Patients with anaplastic astrocytomas are more likely to benefit from chemotherapy than patients with glioblastoma [1319, 918].

A complete response instead of a partial one after radiochemotherapy, as judged by a CT scan, is predictive of longer survival [2359].

Patients with anaplastic astrocytomas, because of the better survival, are more exposed to the risk of damage from aggressive therapies, such as neutrons [1876], the radiosensitizer misonidazole [716], and intracarotid carmustine (BCNU) [3142].

For other therapeutic problems, see Sect. 9.2.2.12.

## 9.2.2

### Glioblastoma Multiforme

#### 9.2.2.1

##### *General Considerations*

Glioblastoma multiforme represents the extreme malignant variant of astrocytic tumors. Among neuroectodermal neoplasias, glioblastoma is the malignant tumor par excellence. Its nosological position has been discussed for a long time, especially as a form distinct from anaplastic astrocytoma. A short historical overview of the problem must be given.

Bailey and Cushing [134] named glioblastoma the malignant glioma, which earlier was labeled spongioblastoma multiforme [133, 2867], to distinguish it from the uni- and bipolar spongioblastomas. This new nomenclature was generally accepted, even though it faced opposition, especially because glioblasts were not well recognized in histogenesis.

Because of its various morphological aspects, this tumor was classified in different ways. For example, Bergstrand [204] distinguished three groups corresponding to three different aspects: multiforme, fusiform, and protoplasmic. Busch and Christensen [404] instead preferred the subdivision into angionecrotic, multicellular, and magnocellular types.

The nosological position of this tumor was overturned with the classification of Kernohan et al. [1661], who abolished it as a tumor entity and put it in the group of

grade 4 astrocytomas. There is no doubt that glioblastomas arise through a process of anaplasia from astrocytomas, but it cannot be said that this is an absolute rule. Sometimes, no sign indicating the preexistence of an astrocytoma is found. Therefore, the necessity of retaining glioblastoma as a tumor entity was emphasized even considering anaplasia [2793, 2899] and that it can develop so rapidly as to erase any trace of a preceding astrocytoma.

A powerful contribution to the problem of the relationships between astrocytoma and glioblastoma was brought by Scherer [2984]. He distinguished the rarer primary glioblastomas and the more frequent secondary glioblastomas, derived from astrocytomas. This point of view later found wide consensus [1297] and the concept was extended to other oncotypes, so that glioblastoma was thought to represent the final malignant pathway common to astrocytomas, oligodendrogliomas, and also ependymomas [2793, 1297].

### 9.2.2.2

#### *Frequency, Age, Site and Clinical Features*

Glioblastoma is the most frequent neuroepithelial tumor. Its peak of frequency is the fifth and sixth decades of life, and there is a slight male predilection [2994, 1520, 3595, 3803]. It is very rare in patients below 30 years of age. Glioblastomas represent, in the personal series, 68.4% of all gliomas and 31.6% of all intracranial tumors.

This tumor is located mainly in the white matter of the cerebral hemispheres, and its sites of predilection are: frontolateral, frontodorsal, and frontobasal; temporolateral and temporomedial; parietodorsal and parietolateral; occipitodorsal; basal ganglia; thalamus; corpus callosum [3799]. During tumor growth, such locations may obviously merge. For example, a glioblastoma of the basal ganglia is often also temporal; a frontal one may invade and cross the corpus callosum, expanding in the opposite hemisphere as a “butterfly” tumor. Temporal tumors diffuse more easily anteroposteriorly.

Diffusion may be facilitated in the white matter by long fiber tracts such as longitudinal fasciculi, uncinate fasciculus, corona radiata, and optic radiation. Tumors which invade the internal capsule tend to grow deeply, whilst the thalamic ones do not usually go beyond the internal capsule [2157]. It has to be noted that often the infiltration of a fasciculus is only noted microscopically [2990]. The cerebellar location is very rare (see Sect. 9.3.5.6).

The greater frequency in males suggested a possible hormone dependence of the tumor. This would be consistent with what has been observed in spontaneous murine gliomas [949] and with steroid receptors [2657]. Experiments on a cell line of human glioblastoma transplanted into athymic mice demonstrated that cell growth is facilitated in males and that androgenic receptors are found mainly in males [3542]. Glucocorticoid and especially androgen receptors have been demonstrated to be present in glioblastoma, more frequently in females than in males [2555].

The clinical symptomatology is characterized by site-specific signs and by signs of increased intracranial pressure. The latter are produced more by the tumor volume

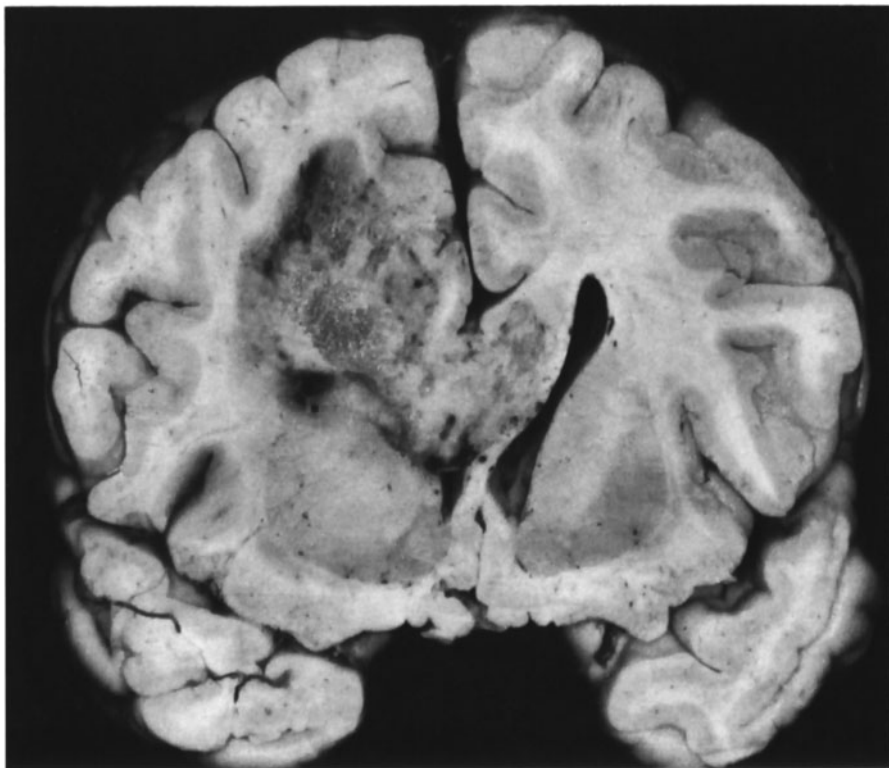


Fig. 9.13. Glioblastoma invading the corpus callosum

and peritumoral edema than by hydrocephalus. Among the site-specific signs, seizures are included whose type depends on the location of the tumor. The most frequent sign is hemiparesis [2928]. Signs and symptoms may develop progressively, but not infrequently there is an acute presentation with epileptic seizures. Usually the preoperative history is of some months, during which subtle personality changes and memory loss take place. Sometimes the acute onset of symptomatology is due to an intratumoral hemorrhage.

#### 9.2.2.3

##### *Macroscopic Appearance and Imaging*

In general, the tumor features a large expanding mass infiltrating the white and gray matter (Figs. 9.13–9.15). On the cut surface the color varies depending on the regressive events which have occurred: from reddish to bluish or from gray to yellow due to necroses. Very often, small cysts are visible. The consistency may vary from creamy in necrotic areas to hard in scarred ones. The tumor may not be seen on the cortical surface, but the gyri may be widened, swollen, or reddish due to small hemorrhages.



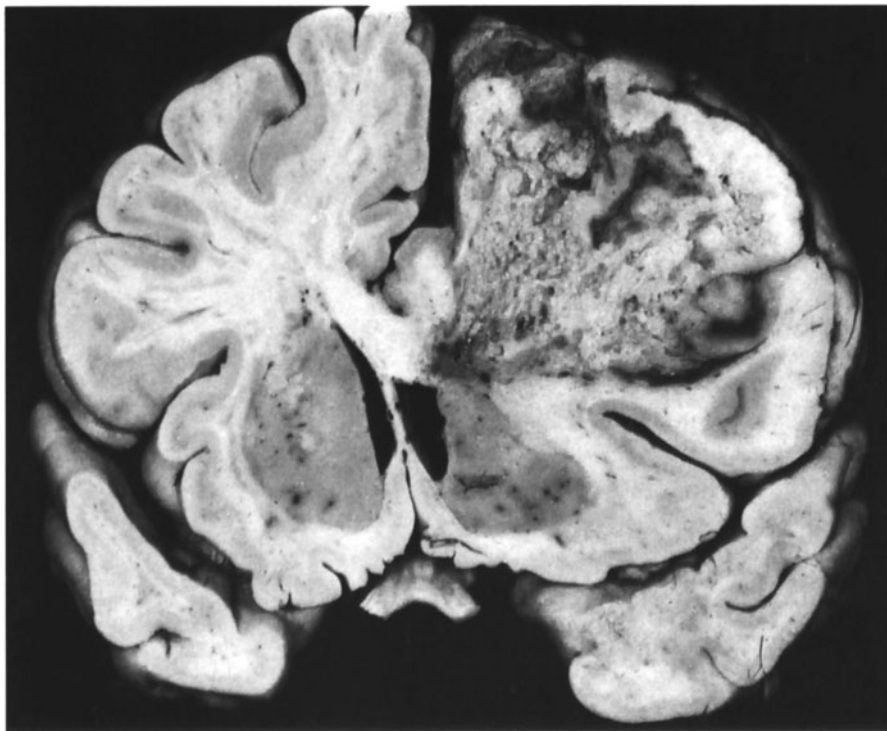


Fig. 9.14. Frontal glioblastoma

Glioblastoma is not uncommonly multicentric (Fig. 9.16), but sometimes the multicentricity is only apparent because macroscopically visible proliferation centers are actually connected by tumor proliferations which are only microscopically detectable.

The main feature on CT scan is contrast enhancement. Typical is the ring-shaped aspect with a hypodense center due to necrosis and a peritumoral hypodense area due to edema (Fig. 9.17). The absence of contrast enhancement is not typical of glioblastoma; however, it does not exclude the diagnosis. The classical aspect with the ring-shaped contrast enhancement gives rise to problems in differential diagnosis with abscesses and metastatic tumors.

On MRI, the tumors characteristically show low signal intensity on T1-weighted and high signal intensity on T2-weighted images. Hemorrhages may be present, but calcifications are uncommon. It is very important to recognize the tumor edge either on CT or MRI for surgical and prognostic implications. Angiography is less useful than it used to be; it shows vessel displacement and increased vascularity of the tumor. FDG-PET and single photon emission CT (SPECT) scanning with thallium-201 may provide specific additional information.

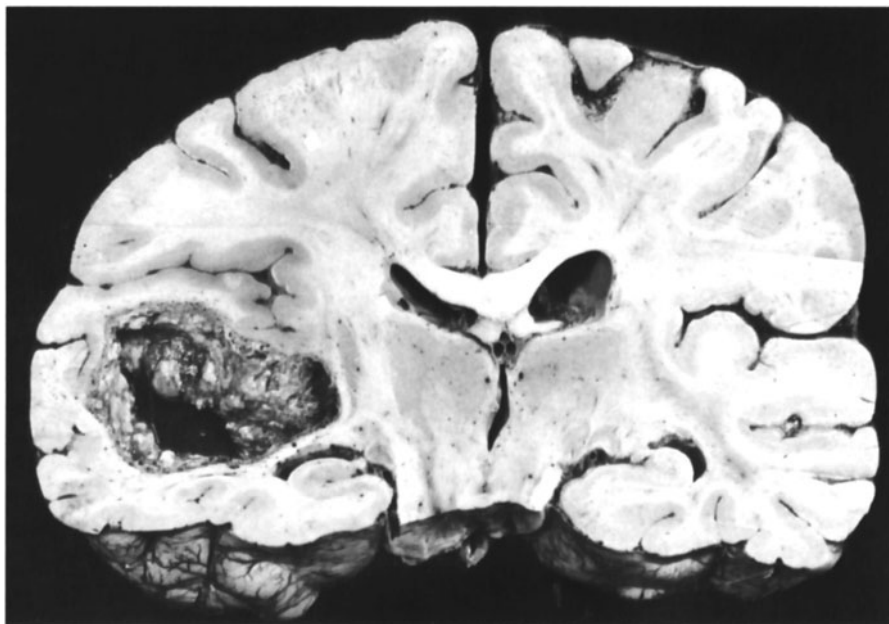


Fig. 9.15. Temporal glioblastoma

#### 9.2.2.4

##### *Microscopic Appearance*

In all the reports, glioblastoma is presented as the most polymorphous glioma [3799, 2899, 2901, 2994, 400], and its astrocytic character is not always diffusely present. Generally, there is a marked cellular density and nuclear pleomorphism (Fig. 9.18a). Besides areas of packed cells with almost isomorphous nuclei, there are others showing monstrous nuclei, multinucleated cells, and intranuclear inclusions (Fig. 9.18b). The cytoplasm can be of different sizes, round, elongated, and variably GFAP positive or negative. Mitoses are very abundant, prevailing in the less polymorphous and in the more densely cellular areas.

The highly proliferating areas are characterized by densely packed cells with scanty cytoplasm, mostly GFAP negative [668, 389, 3024], and show many mitoses. These areas are especially evident in cortical invasion (Fig. 9.19). Necroses are a characteristic feature of glioblastoma. They may be extensive and centrally located (Fig. 9.20) and of medium size with partial palisades or small with complete pseudopalisades (Fig. 9.21a). The latter may be numerous and sinuous in shape. Whilst the former are in general caused by the occlusion of blood vessels by thrombosis, the latter derive from highly packed proliferating growth centers without an adequate blood vessel supply [3017, 3030]. Large necroses are the fundamental element which distinguishes glioblastoma from anaplastic astrocytoma.

Another typical feature of glioblastoma is represented by the abundant blood vessel supply. The prominent production of reticulin is in relation to the vessels

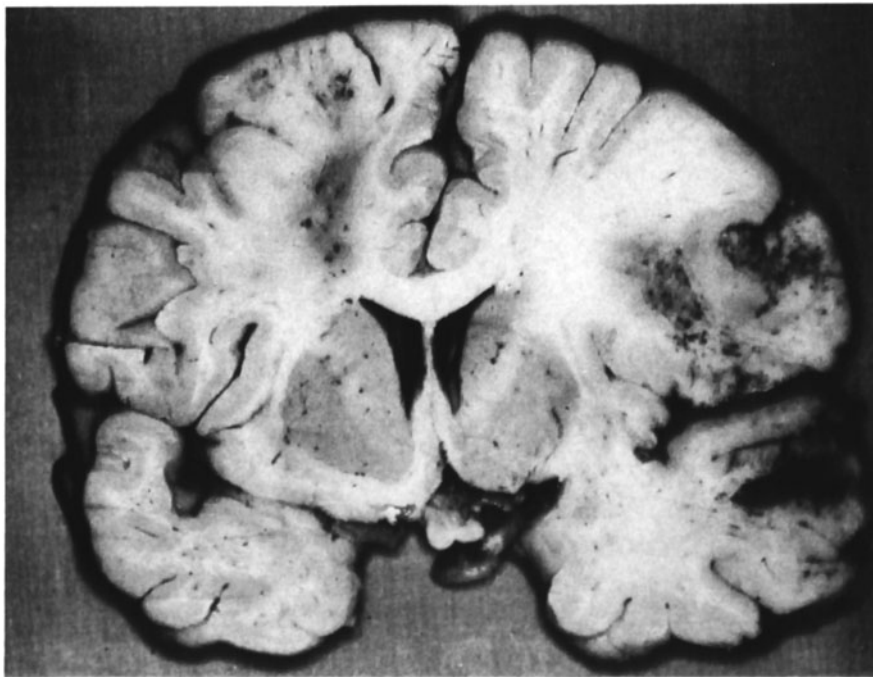
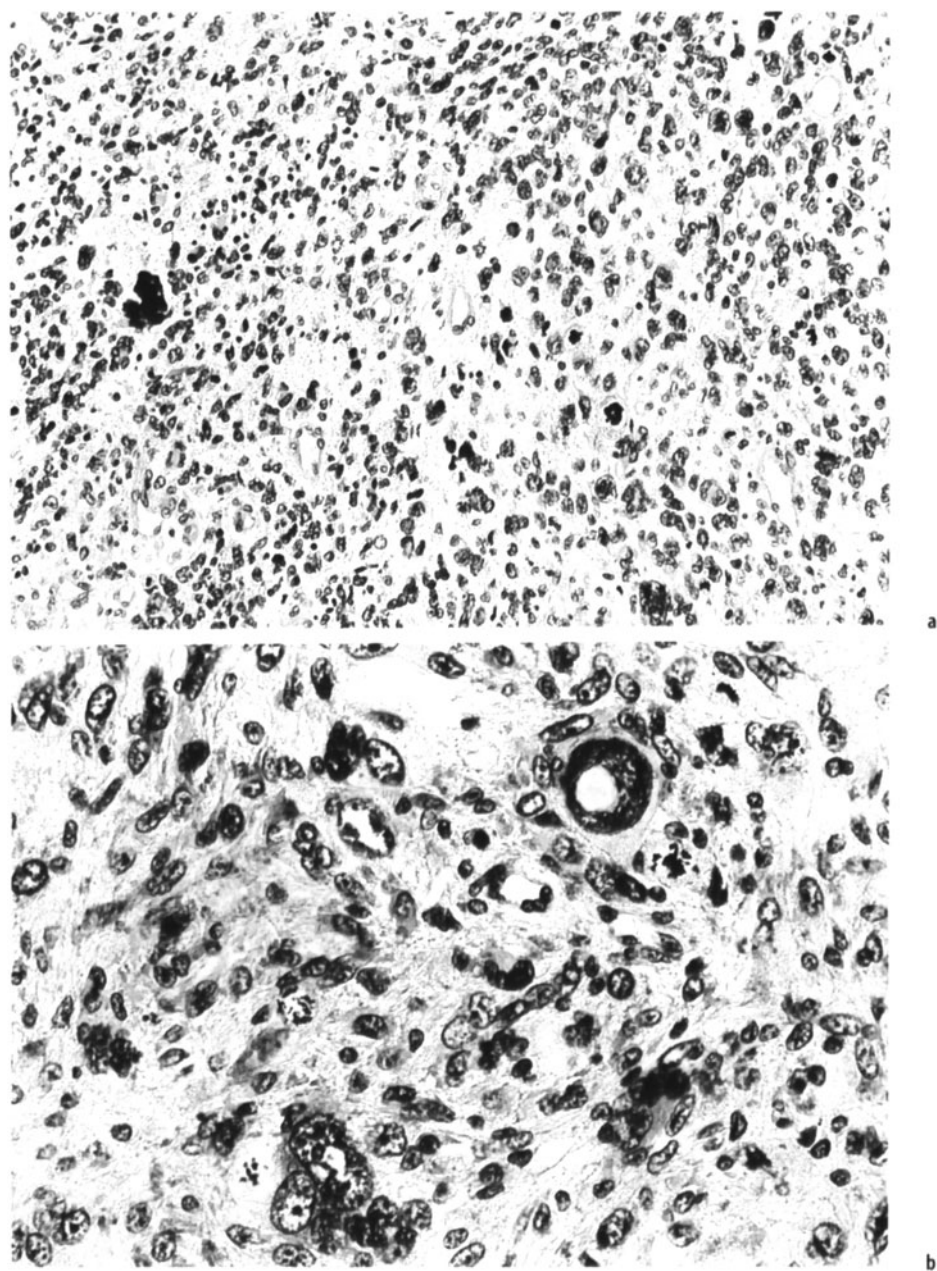


Fig. 9.16. Multicentric glioblastoma



Fig. 9.17. Glioblastoma, typical aspect on computed tomography (CT)



**Fig. 9.18a,b.** Glioblastoma. **a** Nuclear polymorphism with many mitoses, also atypical ones. H&E,  $\times 200$ . **b** Nuclear inclusions. H&E,  $\times 400$

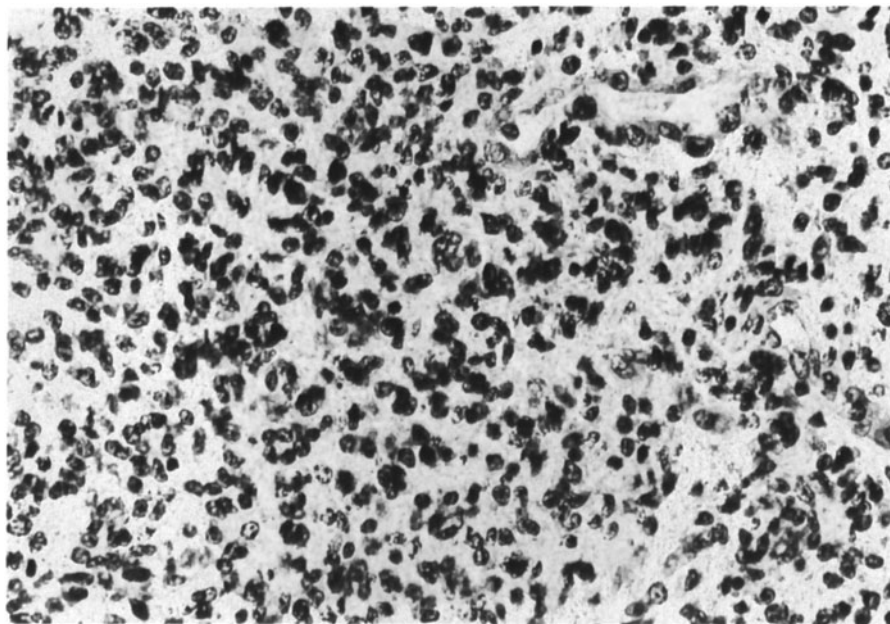


Fig. 9.19. Glioblastoma, invasive area with high cell density and also isomorphic nuclei. H&E,  $\times 300$

(Fig. 9.21b). Dilated and neoformed blood vessels are common, and endothelial proliferations involve capillaries, arteries, and veins, sometimes also the meninges. Glomeruloid formations arise, formed by endothelial hyperplastic cells with an embryonal appearance (Fig. 9.22). Sometimes the formations can be arranged like a “wall” towards normal tissue, necroses, etc. (Fig. 9.23a). The significance of endothelial proliferations has long been discussed [875, 3585, 3644]. In personal experience, the cortical vascular tree formed by the arteries penetrating from the meninges and by their collateral branches responds to tumor infiltration with endothelial hyperplasia which leads to its distortion and impairment of its functions. Circumscribed areas of necrosis arise due to local ischemia. Vascular glomeruli can also form in the healthy cortex around the tumor, but in personal experience, this happens when the overlying meninges are infiltrated. It has to be remarked that endothelial hyperplasia in glioblastoma is a phenomenon which does not precede but follows cortical tumor infiltration, and it is not synonymous with neovascularization [3030].

The blood vessels increase in caliber towards the center of the tumor. In this position there is usually a large area of central necrosis, and between this and the peripheral proliferative zone there are large and deformed blood vessels with thickened walls, sometimes featuring degenerative changes and often thrombosis.

The blood vessel network can be highlighted with techniques which stain the basement membrane, such as the immunohistochemical demonstration of laminin (Fig. 9.23b) [1079, 2199] and of type IV collagen [2477]. Generally, the membrane between the glial cells and adventitia remains relatively preserved.

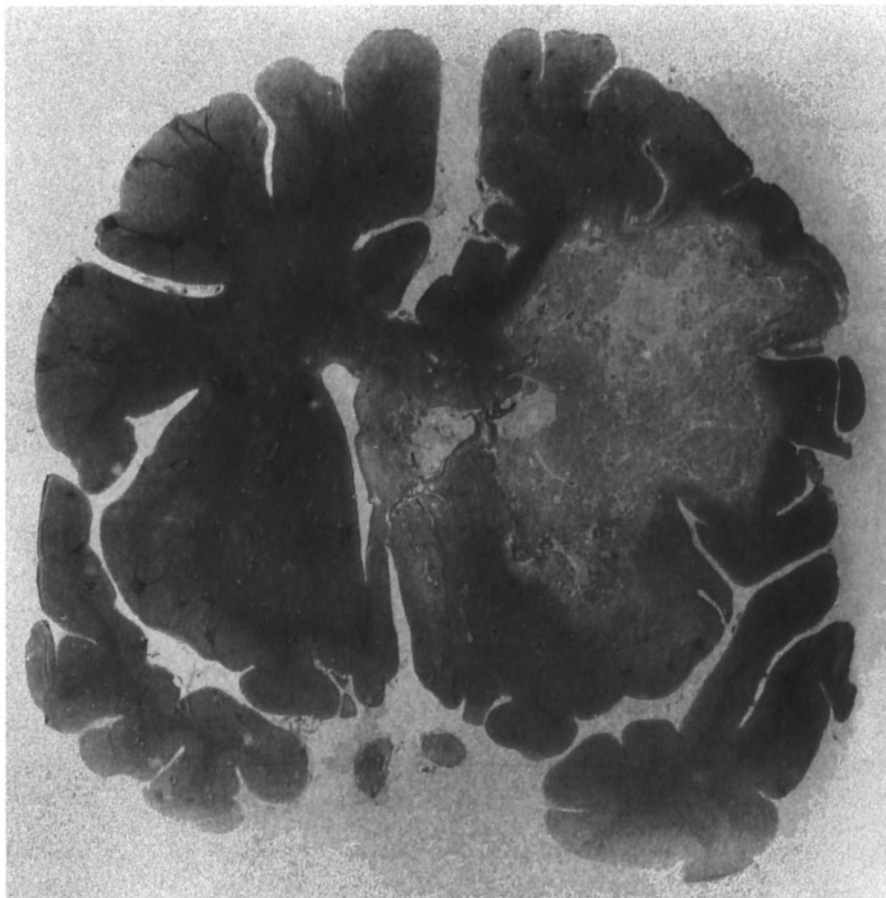
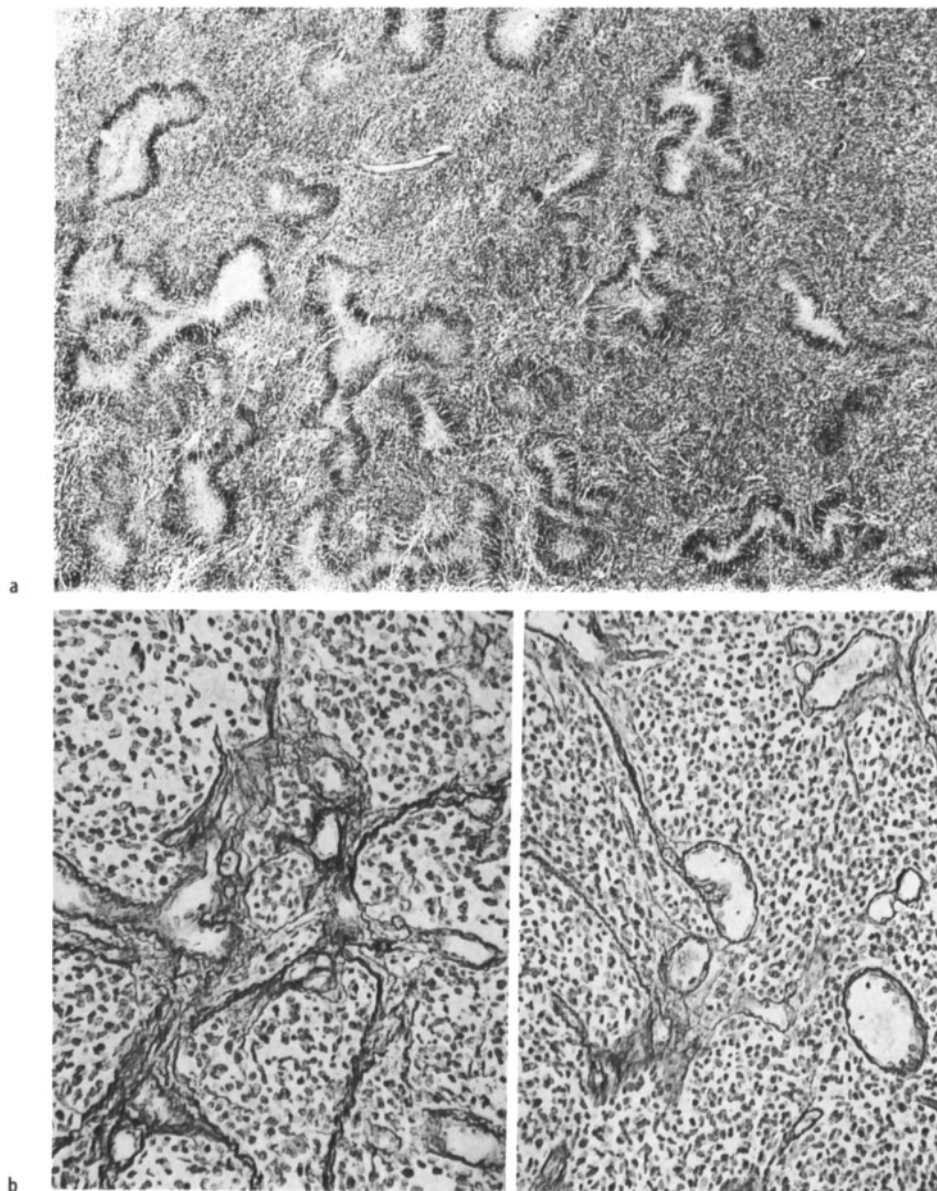


Fig. 9.20. Glioblastoma, extensive central necrosis. H&E,  $\times 1$

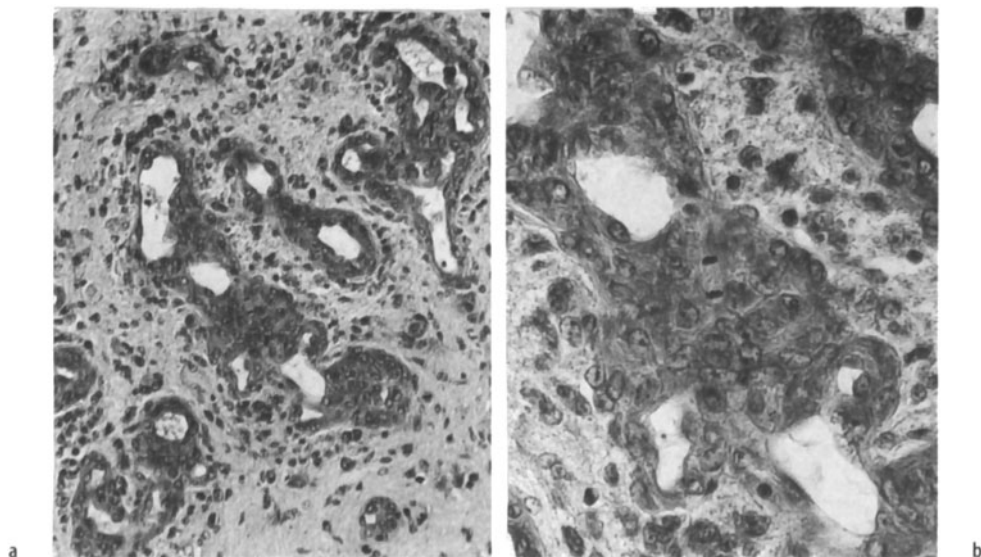
The stromal component of a glioblastoma may be very active and show neoplastic features of the sarcomatous type. Apart from this transformation, which will be expanded upon later, some stromal peculiarities may be found. A rhabdomyoblastic component characterized by elongated cells with elongated nuclei and transverse cytoplasmic cross-striations and originating from the vascular component has, for example, been described. The term “gliomyosarcoma” has been proposed [1124, 157]. Glioblastomas associated with chondrosarcomatous [2785] or osteochondrosarcomatous [2952] components have also been described. All of these features were encompassed in the “ectomesenchymal” hypothesis, which states that neural crest cells may show both neuroglial and mesenchymal characteristics in both the CNS and PNS [773].

The infiltrative growth of glioblastoma leads to invasion of both cortex and white matter. The cells often reach the molecular layer, where they crowd. The subarachnoid spaces may become filled, and the tumor may reinvade the cortex from the subpial re-



**Fig. 9.21a,b.** Glioblastoma. **a** Many circumscribed necroses with pseudo-palisading in a proliferative area. H&E,  $\times 100$ . **b** Abundant reticulin network in relation to blood vessels. Gomori,  $\times 200$ . (From [2994])

gion. Unlike astrocytoma, glioblastoma elicits a strong glial reaction both in the cortex and in the white matter, as revealed by the immunohistochemical demonstration of GFAP which highlights the stubby and long processes of reactive glial cells (Fig. 9.24a).



**Fig. 9.22a,b.** Glioblastoma. **a** Endothelial hyperplasia with mitoses, formation of buds. H&E,  $\times 250$ . **b** Same figure at higher magnification. H&E,  $\times 400$ . (From [2994])

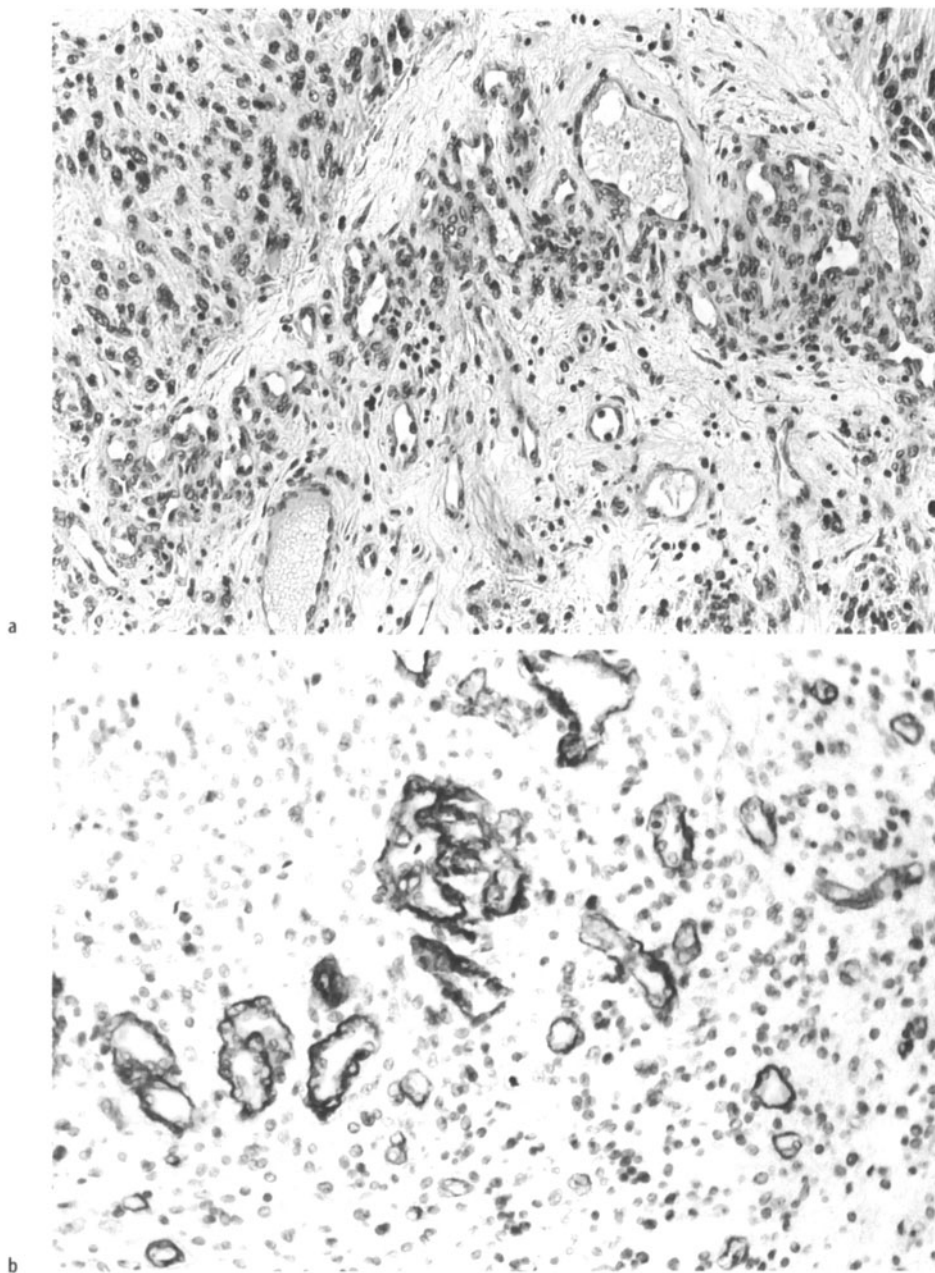
Reactive astrocytes, especially in the cortex, may be included in the advancing tumor and remain visible for a long time amongst the tumor cells (Fig. 9.24b). As has been said, highly proliferating tumor cells are on the whole GFAP negative, so that in many areas there is a mixed cell population which is GFAP positive and GFAP negative. GFAP-positive reactive astrocytes in these areas undergo modifications, even if only due to mechanical factors, and become indistinguishable from tumor cells in as much as they may undergo mitosis [3027]. This fact may lead to the wrong interpretation of the degree of malignancy when the diagnosis is made on small fragments.

Very often, lymphocytic or lymphoplasmacellular perivascular infiltrates are present. They are generally interpreted as indicating an immunologic reaction, because they are associated with a better survival [2170, 351, 2545]. In a series of 199 cases, such infiltrates were observed in 134 patients (67.5%) who survived longer. Infiltrates were more frequently seen in cases which had not previously been treated with steroids [293]. Other studies have, however, not found longer survival in cases with such infiltrates [2788, 3008, 3011, 2852], and doubt has been cast on the specificity of the reaction [3673].

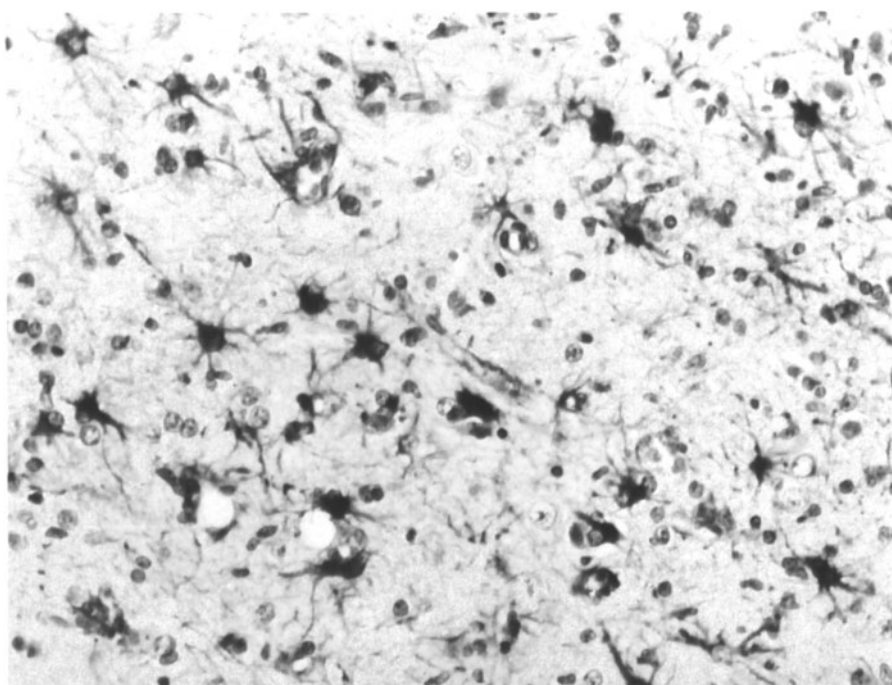
Epithelial growth factor receptor (EGFR) has been demonstrated immunohistochemically in 79% of malignant and in only 9% of well-differentiated gliomas, but also in other oncotypes. However, a correlation with tumor proliferation, as judged with the antibody Ki-67, has not been observed [2754].

By means of in situ hybridization it has been demonstrated that endothelial cells also bear the  $\beta$ -receptor for platelet-derived growth factor (PDGF) and express the mRNA for the PDGF B chain, which implicates them in an autocrine mechanism of stimulation [1304, 2182]. PDGF may, therefore, become a member of the family of angiogenic peptides.

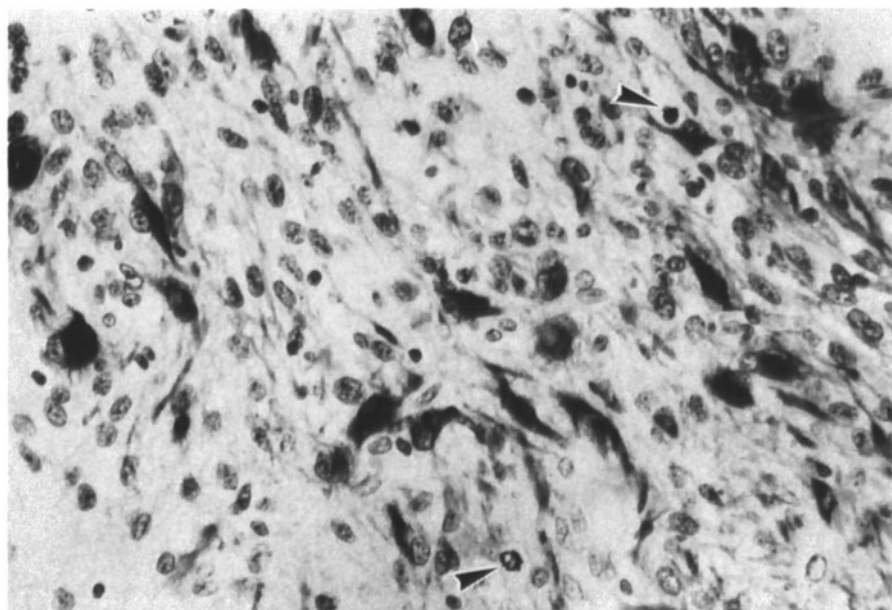




**Fig. 9.23a,b.** Glioblastoma. **a** Wall of vascular glomeruli. H&E,  $\times 200$ . **b** Thickened basement membranes evident with laminin. PAP-DAB,  $\times 200$

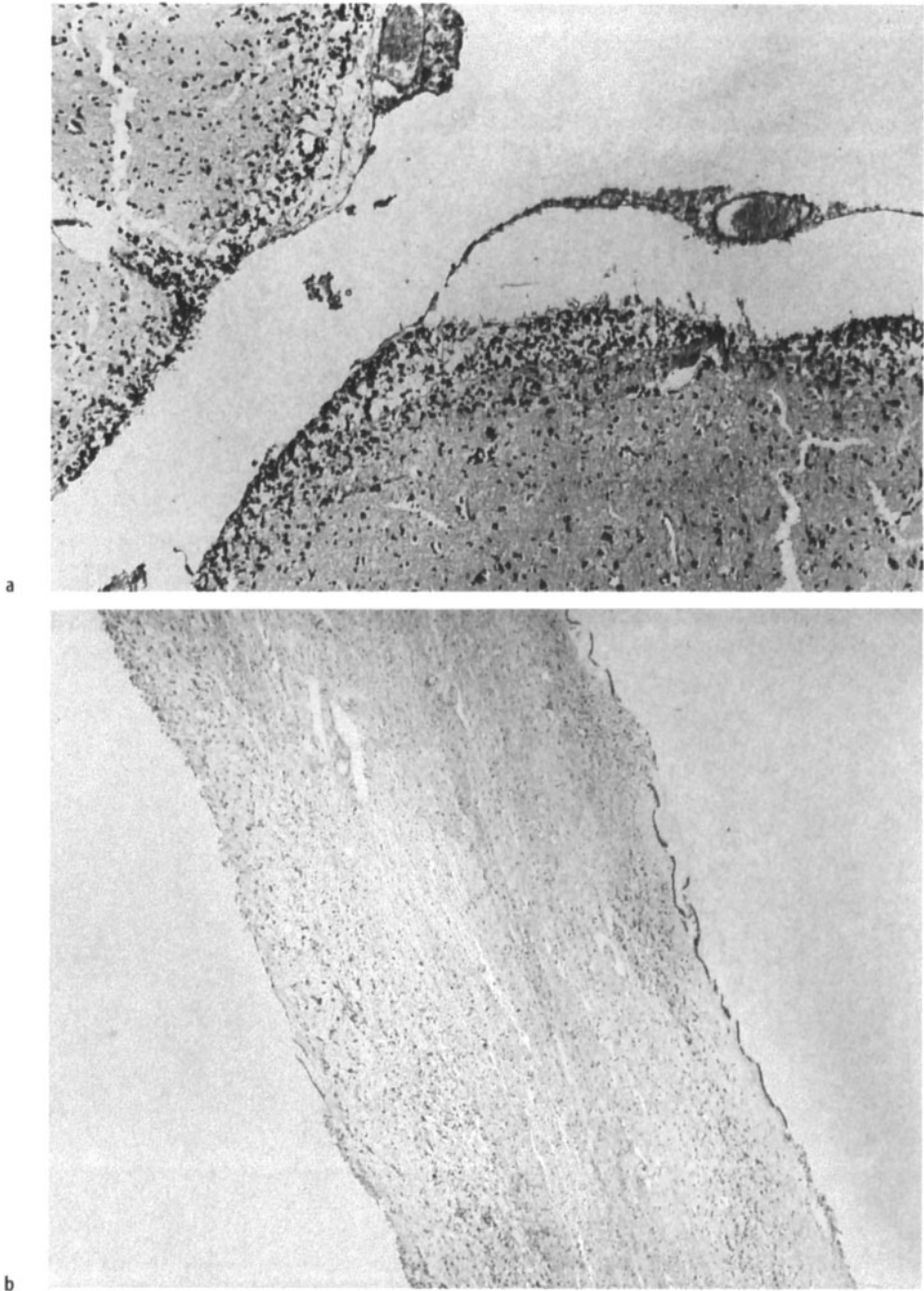


a



b

**Fig. 9.24a,b.** Glioblastoma. **a** Reactive astrocytes in the invaded cortex. GFAP, PAP-DAB,  $\times 300$ . **b** Reactive astrocytes intermingled with tumor cells. Arrowheads indicate mitoses. GFAP, PAP-DAB,  $\times 400$



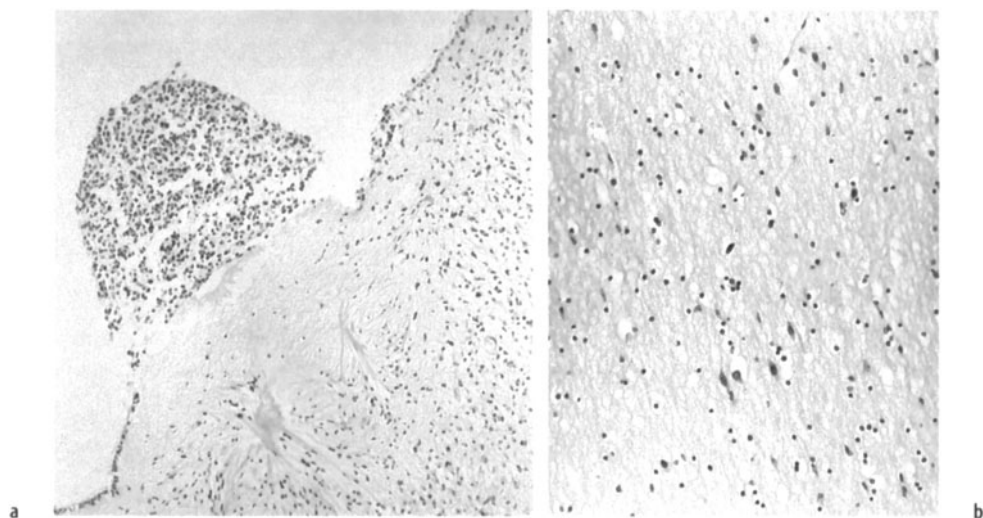
**Fig. 9.25a,b.** Glioblastoma. **a** Subpial growth. H&E,  $\times 200$ . **b** Diffusion along the septum pellucidum. H&E,  $\times 100$

Some data on transforming growth factor (TGF), another factor which is important for neoplastic transformation, are beginning to appear. Two types are known,  $\alpha$  and  $\beta$ . The former shares a remarkable percentage of homology with EGF, and together they compete for the same membrane receptors [257]. TGF- $\beta$  has been observed immunocytochemically both in benign and malignant gliomas [527, 2939], but not in normal nervous tissue, whilst TGF- $\alpha$  has been seen to prevail in malignant gliomas [2939], where it could be related to the progression of the tumor. For further information, see Chap. 2.

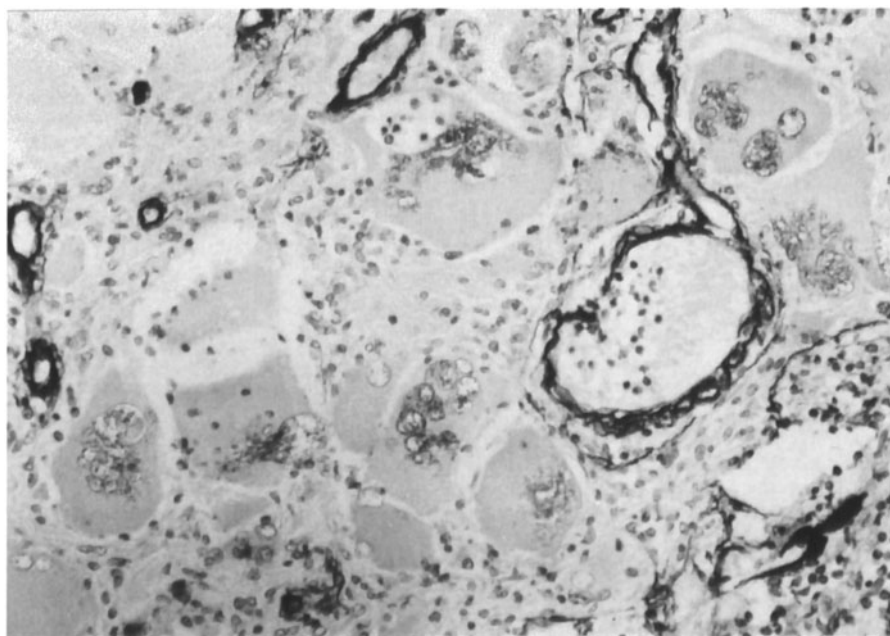
#### 9.2.2.5

##### *Tumor Spreading*

Classically, the tumor grows from the white matter into the cortex, features satellitosis, and reaches the meninges. It may grow in the subpial region and spread to adjacent cortices (Fig. 9.25a). A growth may occur in the subarachnoidal space, and the cortex can be reinvaded (see Fig. 7.6a), or meningeal gliomatosis may occur. Infiltration of the ependyma and of the subependymal layers is also characteristic, with the possibility of further diffusion into the subarachnoid spaces. The subependymal layers may, however, also form a barrier to the tumor. As already stated, tumor spread may take place and be detected only histologically, through fibrous structures such as the septum pellucidum (Fig. 9.25b), hence simulating multicentricity [2990, 2991]. Glioblastoma may diffuse into the ventricular system, colonizing the walls of ventricles (Fig. 9.26a) or even in the region of the cauda equina: blastomatous ependymitis [1253] and meningeal gliomatosis [2662], respectively. These events are, however, not precisely known from the quantitative point of view, because systematic studies are few [3767, 114]. In an autopsy series of 51 glioblastomas, CSF dissemination was found in 14. In seven of these, there was pronounced dissemination and scarce local reaction with a poor expression of GFAP by the tumor cells, and in the other seven there was scanty dissemination and extensive local infiltration with marked GFAP expression. The less differentiated cells could be more easily released into the CSF but are less invasive [2503]. The first proposition has been accepted, because it is in agreement with what is observed in other poorly differentiated tumors, such as medulloblastoma, whilst the second has not been considered as supported by valid correlations [2877]. The most important feature of the spreading of glioblastoma is that invading cells travel along the fiber tracts in the hemispheric white matter (Fig. 9.26b). They can be found outside the hypercellular edge of the tumor, not only in the area usually noted as hypodense on CT scans, but even further. The cells are not easily identifiable on the usual histological preparations, but perhaps it is easier with special stainings on fresh tissue [654]. The invasion assumes a digitating aspect in the long axis of many gyri. The frequency of dissemination is obviously influenced by the "duration" of the tumor. The location on the walls of the ventricles may also depend on local ependymal defects, which are frequent and extensive, due to the hydrocephalus which often accompanies the tumor [2435]. Diffusion via the CSF can also reach the cerebellum, where secondary growth may occur. It seems that spread via the CSF is more frequent in children [1583], and this could have some importance in the establishment of radiotherapy treatment modalities.



**Fig. 9.26a,b.** Glioblastoma. **a** Colonization on the ventricular wall. **b** Infiltrating cells in fiber tracts of the hemispheric white matter. H&E,  $\times 200$



**Fig. 9.27.** Giant-celled glioblastoma. H&E,  $\times 200$

### 9.2.2.6

#### *Differential Diagnosis*

A differential diagnosis has to include, apart from anaplastic astrocytoma, metastatic carcinoma, cerebral lymphoma, ependymoma, sarcoma and pleomorphic xanthoastrocytoma. In respect to carcinoma, distinction is based on the mode of infiltration of glioblastoma, which contrasts with the sharp edge between normal tissue and the carcinoma; on the appearance of necroses with pseudo-palisades which are different from the interval necroses of carcinoma; and on the peculiar and exuberant endothelial proliferation. In particular cases, the differential diagnosis is not easy, especially if only small areas of tumor are examined. The possibility of the formation of papillae represented by columnar cells resting on a delicate vascular-connective stroma [2330] and simulating medulloepithelioma or adenocarcinoma has to be taken into account. These papillary formations may represent an epithelial-sinusoidal differentiation or resemble an ontogenetic feature. It is also possible to observe foci with squamous differentiation, with the development of epithelial whorls, keratin pearls, and cytokeratin positivity, which represent extreme degrees of epithelial differentiation [2331].

Lymphoma is essentially distinguished by its intra-advential growth, especially at its periphery, as highlighted in reticulin preparations. Sarcomas generally show abundant reticulin and totally lack GFAP. Ependymoma is recognizable if its characteristic tissue elements, such as perivascular radiated crowns, rosettes, and canals, are present. The pleomorphic xanthoastrocytoma does not usually show mitoses or circumscribed necroses [3794].

Cases have been described, considered as variants of glioblastoma, which are characterized by the presence of strongly lipidized, GFAP-positive cells, besides necroses and mitoses [1647]. These tumors are usually deeply situated [1061], but they have also been described in superficial locations. Because of the above mentioned features, they are different from pleomorphic xanthoastrocytoma.

### 9.2.2.7

#### *Giant Cell Variant*

The giant cell variant is characterized by numerous large, giant cells with polymorphous nuclei and is otherwise not different from classic glioblastomas (Fig. 9.27). Despite the importance of polymorphism, they show a reduced proliferative potential [1405] and a longer survival [181, 390, 1065, 2197]. The existence of this variant [2871, 2903] has long been contested because tumors with monstrous cells have for a long time been diagnosed as “monstrocellular sarcomas” [3799]. For the differential diagnosis from gliosarcoma, see Sect. 9.2.2.8. There is no doubt today that this variant exists. In addition to the features indicated above, it is characterized by a lack of endothelial proliferations and by the presence of circumscribed necroses without pseudo-palisades [400]. The tumor is usually circumscribed on CT scan and occurs preferentially in the temporal lobe [2108].

### 9.2.2.8

#### *Gliosarcoma*

*General Considerations.* The occurrence of a mesodermic component in neuroepithelial tumors, and specifically in gliomas, has always been a challenging problem to which different solutions have been given over the course of time. The mesodermic component is not necessarily neoplastic. Five categories have been suggested [464]: (1) meningeal reaction to infiltrating gliomas, (2) desmoplastic responses of meninges, (3) scars in glioblastomas, (4) confluent thickened vessel walls due to extravasated plasma proteins, (5) neoplastic nature. The last category includes gliofibroma and gliosarcoma.

The term gliosarcoma was first used by Stroebe [3325], but it only really began to be applied with the fundamental work of Feigin and Gross [873] and was subsequently widely accepted [875, 2307]. Cases with sarcomatous growth prevailing over the glial one have been described, a feature commonly found in cultures [1189]. A large body of opinion holds that the sarcomatous component originates from the proliferating endothelium of blood vessels.

However, contrary observations indicating a derivation from adventitial fibroblasts or histiocytes, or even that the glioma is secondary to a fibrosarcoma, namely “sarcoglioma” [1846], have been made.

The observation of  $\alpha$ -sm-actin positivity in gliosarcoma has been confirmed [2618] and it refers to a previous observation of the same positivity within endothelial hyperplasia in glioblastoma [1210A]. Cells positive for  $\alpha$ -sm-actin can be smooth muscle cells or pericytes

*Frequency, Age, Site.* The incidence of gliosarcoma in respect to malignant gliomas is difficult to calculate because of the multiplicity of the diagnostic criteria. It varies from 1.2% [875, 1731] to 8% [2307]. In our series they represent 6.6%. Gliosarcomas arising from blood vessels in oligodendrogliomas [877, 2564] or in ependymomas [2015] have also been described. The mean age is close to that for glioblastoma, being in 33% [2307] and 50% of cases [2229] over 60 years. The tumor is frequently located in the temporal lobe; however, in one series it was more frequently located in the frontal lobe [2229].

*Macro- and Microscopic Appearance.* The tumor is reddish-gray, has a hard consistency, and is usually well delimited from the surrounding tissues (Fig. 9.28). Two intimately admixed components, a fibrosarcomatous and a glial one, are observed histologically (Fig. 9.29a). The richness in reticulin and the fibronectin-positivity (Fig. 9.29b) of the fibrosarcomatous component and the GFAP positivity of the glial component are fundamental diagnostic elements. In a large series, the mesodermal component was recognized as either a malignant fibrous histiocytoma or a fibrosarcoma [2229]. There is a sharp demarcation between the two formed by a basement membrane (Fig. 9.30a), easily visible under the electron microscope or by immunohistochemical demonstration of laminin [1079]. The blood vessels have different features in the two components. They are similar to those of glioblastoma in the glial component and are “slit-like” and practically without a wall in the sarcomatous part (Fig. 9.30b). The two components sometimes may be so intimately admixed that the glial cells may be seen as isolated elements only by GFAP staining (Fig. 9.31a) or as

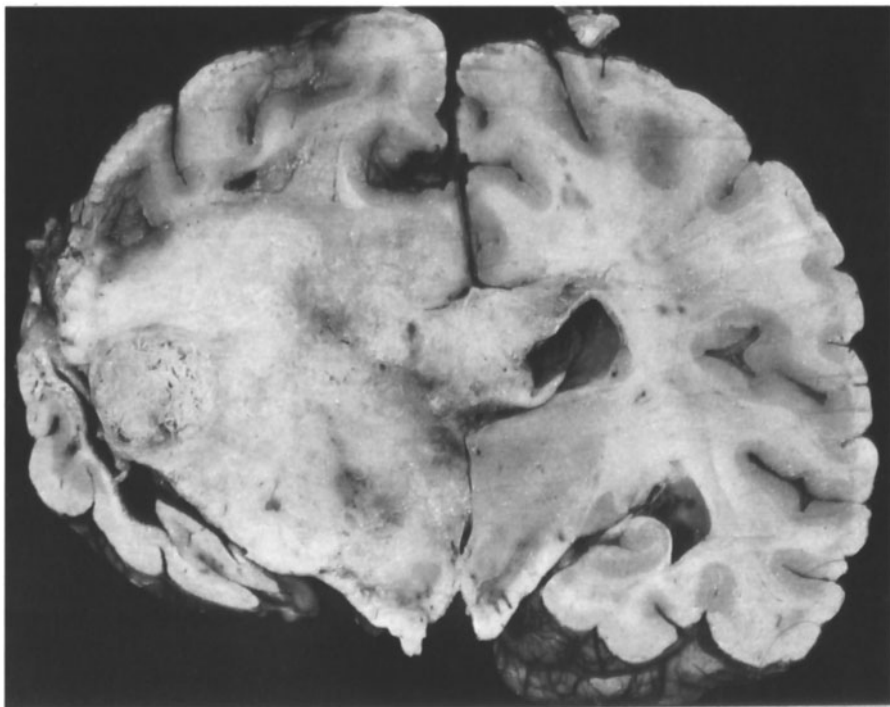


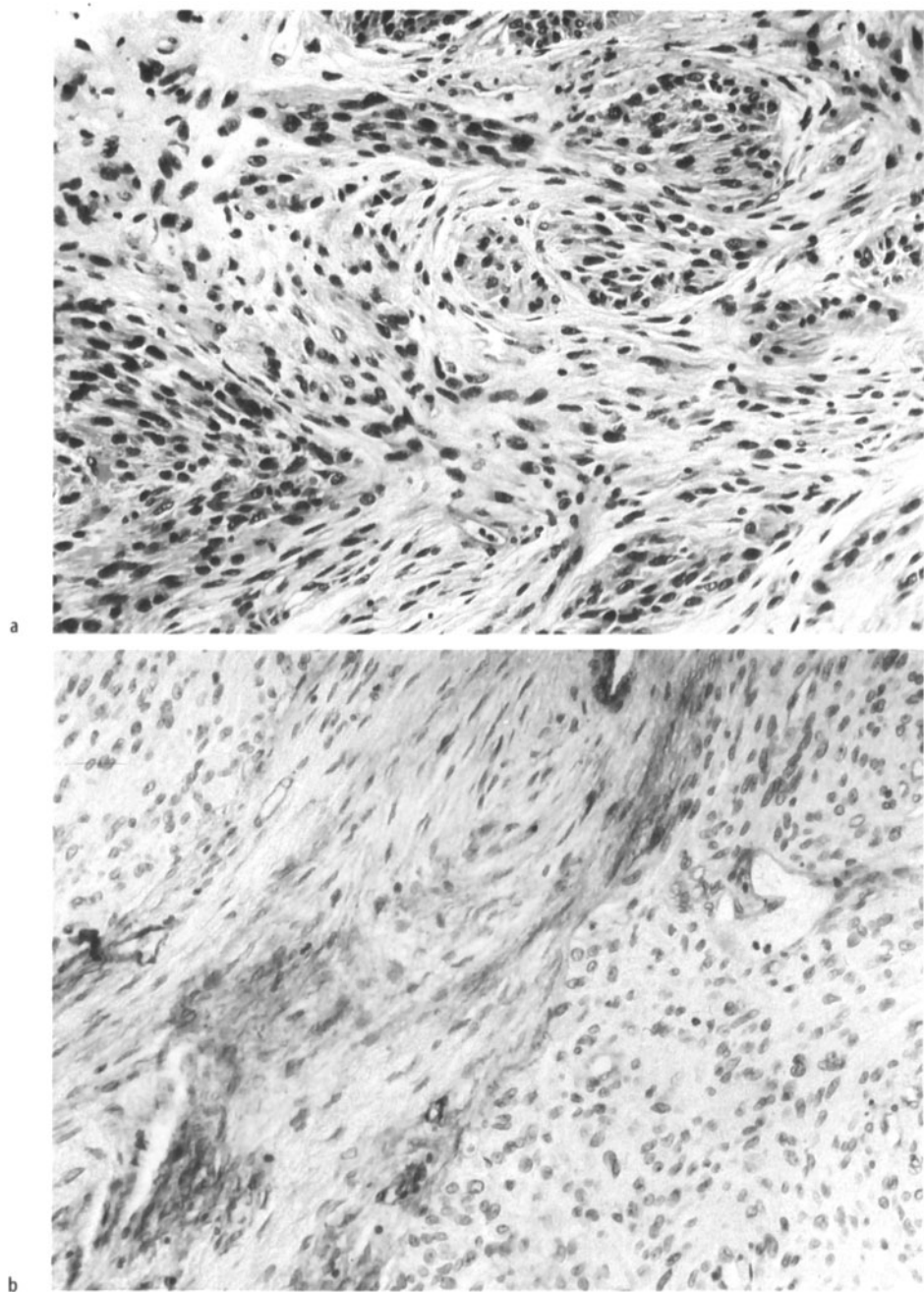
Fig. 9.28. Gliosarcoma. (From [3013])

ribbons narrowed by mesenchymal trellises (Fig. 9.31b) or take up adenoid features and simulate the cells of an adenocarcinoma [1652]. GFAP positivity usually resolves the doubt. A diagnostic complication is the possibility that foci of marked epithelial differentiation will develop from the glial component and present as cytokeratin positive squamous cells and keratin pearls [2331].

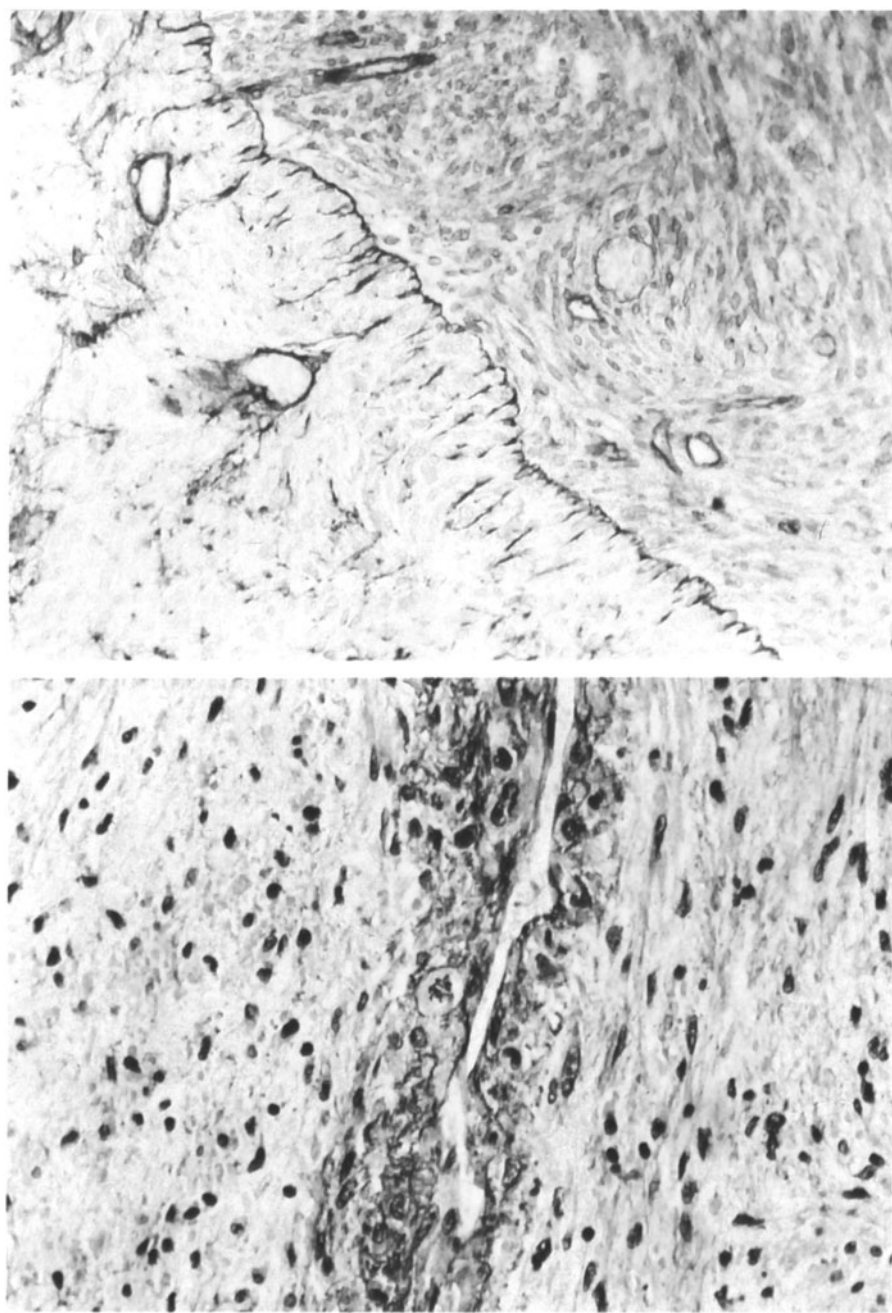
Gliosarcoma raises some biological problems which have only been partially resolved. The first is related to the presence of giant and monstrous cells. Some authors interpret them as being of a glial nature and the tumor a giant cell glioblastoma [181, 2056, 1211, 2903]. Others considered these cells to be sarcomatous and name the tumor “circumscribed monstrocellular sarcoma of blood vessels” [3799, 1342, 256, 359]. With the immunohistochemical demonstration of GFAP, it has been found that the great majority of giant cells are glial, but that there may also be giant cells in the sarcomatous component. Therefore, “monstrocellular” might not be an inappropriate term, because giant cells do occur. However, it is now obsolete, because giant cells have been proven to be glial [3013].

A problem that is still debated is that of the origin of the mesodermic component. One of the first hypotheses was that of the origin from hyperplastic endothelia of glioblastoma [875, 3020, 3224]. However, it was observed that factor VIII/RAG is positive in the glomeruli of glioblastoma, but only in the cells delimiting the lumina [2202], and negative in the fibrosarcomatous cell populations of gliosarcoma.

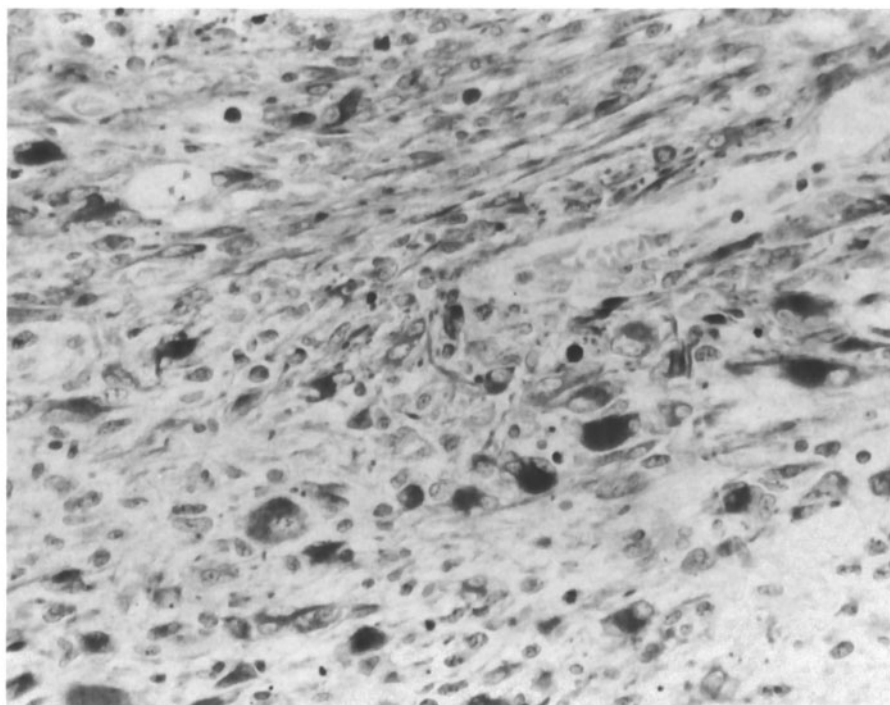




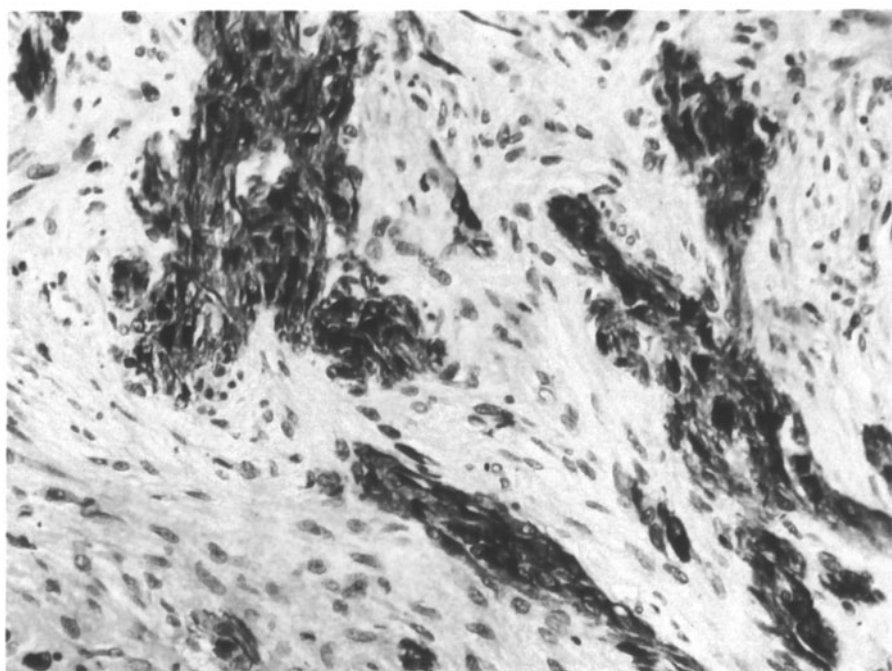
**Fig. 9.29a,b.** Gliosarcoma. **a** Glial and fibroblastic proliferations are almost indistinguishable. H&E,  $\times 300$ . **b** The mesodermic component is fibronectin positive. PAP-DAB,  $\times 200$



**Fig. 9.30a,b.** Gliosarcoma. **a** Basement membrane separates the two components. Laminin, PAP-DAB,  $\times 200$ . (From [3020]). **b** Vessel with slit-like lumen in the mesodermic component. H&E,  $\times 300$



a



b

These must therefore originate either from pericytes or fibroblasts or even from endothelial cells which have lost the capacity to express factor VIII/RAG. Sometimes it is possible to see a transition between factor VIII/RAG-positive endothelial cells of glomeruli and factor VIII/RAG-negative fibrosarcomatous proliferations [3020, 3224]. It is possible that, in the process of neoplastic transformation, the endothelial cells lose the capacity to express the marker, as has been observed in other conditions, e.g., angioreticuloma [1182]. Some evidence has been accumulated against this hypothesis.

An alternative interpretation based on the demonstration of histiocytic markers such as  $\alpha_1$ -antichymotrypsin, lysozyme, and  $\alpha_1$ -antitrypsin, which are abundant in the sarcomatous component, is that the adventitial histiocytes are the major source of the fibrosarcomatous proliferation [1731]. Taking into account that the histiocytes are positive for fibronectin [634] and are more concentrated around blood vessels than in fibrosarcomatous areas, it is possible that they themselves are potential fibroblasts [979] which may promote the proliferation of mesenchymal cells such as fibroblasts or endothelial cells [1731]. However, the positivity for antiproteases and monocyte/macrophage series markers in the mesenchymal areas does not seem sufficient to establish the histiocytic nature of the tumor. The mesenchymal component may derive from fibroblasts or from undifferentiated mesenchymal elements of the blood vessel adventitia [1155]. In the fibroblastic proliferations which originate from blood vessels in irradiated glioblastomas, collagen type III, typical of fibroblasts, is expressed with fibrils which under the electron microscope seem to be produced by endothelial cells [3031].

The study of the various types of collagen has brought useful information on this point. For example, collagen type IV, typical of basement membranes, is also found in glioblastomas. It can be found in vascular buds, but never in fibroblastic-type proliferations such as those found in gliosarcoma. On the contrary, the latter proliferations express collagen type VI, which is typical of interstitial microfibrils but is never found in endothelial proliferations [2579]. These data do not confirm the endothelial origin of the fibroblastic proliferations. The finding of collagen type VI in the pial-glial basement membranes [2204] might simply be due to adjacent phenomena. In fibrosarcomas arising after the irradiation of glioblastomas, a diffuse histiocytic character is observed, as is also found in fibroblastic meningiomas with which the tumors have been likened [2486].

Two recent observations on the nature of gliosarcomas must be quoted. One refers to the immunohistochemical positive staining for  $\alpha$ -sm-actin of spindle and polygonal cells, which are GFAP negative, suggesting that gliosarcoma represents one end of the spectrum of glioma induced vascular smooth muscle proliferation [1210].

It has been observed that positivity for  $\alpha_1$ -antitrypsin and  $\alpha$ -sm-actin in mesodermic areas is mutually exclusive; thus two different origins of gliosarcoma can be envisaged: smooth muscle cells within glioblastoma or multipotential progenitor cells [2618].

The second interpretation refers to the mesenchymal areas of gliosarcomas as representing astrocytes that have assumed a spindle cell morphology preserving

< Fig. 9.31a,b. Gliosarcoma. a Glial fibrillary acidic protein (GFAP)-positive, isolated glial cells in the mesodermic component. b Narrow ribbons of GFAP-positive cells in the mesodermic component. PAP-DAB,  $\times 400$

GFAP-positive staining and are at the same time  $\alpha$ -sm-actin positive [1551]. This interpretation has not been unanimously accepted [2575].

Some peculiar observations have been made in this tumor. A myxoid component, for example, was found in one case and attributed to the transformation of glial cells [1691]. Rhabdomyoblastic [1124, 157], osteochondrosarcomatous [2952], and chondrosarcomatous [2785] metaplasia have been described in other cases. A patient with features of chondroblastic osteosarcoma has also been described [1270].

GFAP-negative cartilage has been found, due not to the transition from astrocytes [1654] but to mesenchymal metaplasia [145].

A rare mixed tumor is "sarcoglioma" [464], composed of a meningeal sarcoma with a transformed reactive gliosis or a sarcomatous reaction of the meninges to an infiltration of glioblastoma [2866, 2903]. The term "sarcoglioma" was actually coined by Lalitha and Rubinstein [1846] to indicate a glioma secondary to a fibrosarcoma.

A rare benign tumor composed of cells that exhibit both GFAP-positive glial and collagen producing mesenchymal cells has been called gliofibroma [965]. Some examples have been reported. The existence of the tumor as an entity is, however, controversial [3068, 3240]. Other cases have been published [2628]. It may be synonymous with desmoplastic astrocytoma or glioblastomas in malignant cases [464].

A recent interpretation is that it is a glial tumor with astrocytes producing reticulin and collagen fibers appositioned to the cell bodies [464]. As a matter of fact, there is a body of evidence that astrocytes can produce basement membranes and collagen, as it happens also in pleomorphic xanthoastrocytomas.

Of particular interest are the results of immunohistochemical demonstration of p53. It is positive in both components, indicating the origin of glial and sarcomatous components from a common progenitor [28]. Moreover, it has been demonstrated that the two components carry identical mutations (exon 5; codon 151, CCC to TCC; codon 173, GTG to GTA). A common origin is thus possible from neoplastic glial cells [235].

*Prognosis.* The prognosis of gliosarcoma grossly overlaps with that of glioblastoma in many series, with possibly a greater number of cases with longer survival. There is some tendency to leptomeningeal spread.

### 9.2.2.9

#### *Blood Vessel Architecture and Angiogenesis in Gliomas*

In well-differentiated hemispheric astrocytomas there is no neoformation of blood vessels. The tumors utilize the preexisting blood vessels and modify them. In pilocytic astrocytomas of the midline, especially of the cerebellum, but principally in glioblastoma, there are very important changes due essentially to the endothelial hyperplasia leading to the formation of glomeruli. In glioblastoma, three zones may be distinguished for blood vessels: a peripheral zone, rich in neoformed vessels with endothelial proliferation; an intermediate one featuring larger dilated vessels; and a central necrotic one with degenerated large vessels.

The intensity of vascularization cannot always be used as an indication of malignancy. A positive correlation, for example, exists for hemispheric astrocytic gliomas but not for those of the midline or for cerebellar ones. Precise morphometric measurements have demonstrated that an oligodendroglioma can be more vascularized

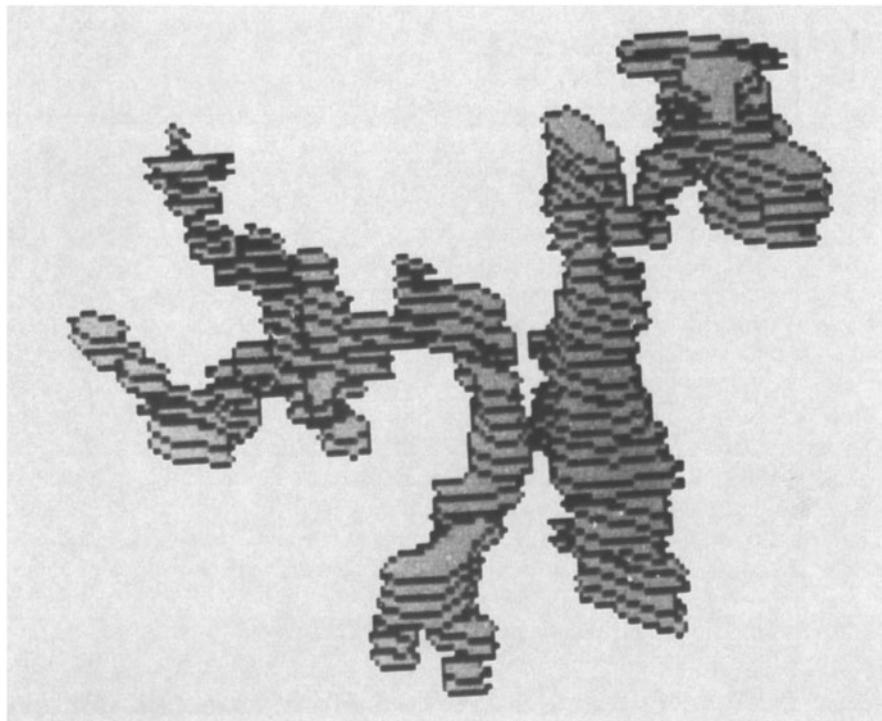
than an anaplastic astrocytoma. This means that the richness in blood vessels depends also on the type of tumor [3116].

Most studies of blood vessels have focused on the difference between normal and tumor blood vessels and capillaries. Normal capillaries are characterized by a continuous basement membrane and by endothelial cells with tight junctions, except in some areas, such as the area postrema and choroid plexus, where the junctions are of the fenestrated type. Endothelial cells have scarce pinocytotic vesicles, and the pericapillary space is small and free from collagen and fibroblasts, because the basement membrane is in direct contact with that of the astrocytes [1330, 3585]. Pericytes may occasionally be present [2007]. Tumor capillaries are completely abnormal: The lumen is wider, there are more endothelial cells with a greater number of junctions and more pinocytotic vesicles, and the basement membrane is thickened by collagen in the pericapillary space [3585]. There are different degrees of endothelial attenuation with fenestrations and opening of the junctions. Typical features of malignant gliomas are blood vessel thrombosis and endothelial proliferation.

Endothelial cells increase in number, feature mitoses, and modify the blood vessels, which become tortuous and glomeruloid. The study of the transition between the normal tissue, infiltration zone, and tumor has demonstrated that endothelial cells progressively increase in number and acquire immature features such as a paucity of organelles and a high nucleocytoplasmic ratio [3644]. Clusters of immature capillaries similar to the normal ones which appear during development [421] and immature buds with a slit lumen and single basement membrane [3643] form in the transition zone.

The endothelial proliferation has been considered, on one hand, as a source of new capillaries and, on the other, as a consequence of vessel thromboses [3318, 425]. A particular relationship seems to occur between endothelial proliferations and circumscribed necroses. It has been hypothesized that endothelial proliferations may represent a response to necrosis. On the other hand, circumscribed necroses may be due to the imbalance between the proliferative potential of the tumor and endothelial cells [1407, 1174]. Morphometric and three-dimensional reconstruction studies have demonstrated that glomeruloid formations represent an extreme degree of deformation of the cortical vascular tree due to endothelial proliferation (Fig. 9.32). The vascular tree becomes inadequate to nourish the increasing number of neoplastic cells, hence the necrosis (Fig. 9.33b) [3030]. The neoplastic invasion of the cortex induces the hyperplastic response of the endothelial cells. New, small blood vessels are formed by sproutings (Fig. 9.33a) [2361] and only occasionally enrich the infiltrated zone with capillaries. Endothelial proliferation is thus not synonymous with angiogenesis, which does not precede but follows tumor infiltration. The endothelial cells within the tumor are also rich in Weibel–Palade bodies [1810], which are usually rare in normal endothelium. There is also a distinct but unimportant participation of  $\alpha$ -sm-actin-positive pericytes to the process of endothelial hyperplasia (Fig. 9.34a) [3030]. Proliferated endothelial cells are immunohistochemically positive for factor VIII/RAG, but only those lining the vessel lumen (Fig. 9.34b) [3643]; however, by immunoelectron microscopy study it can be demonstrated that cells far from the lumen also contain Weibel–Palade bodies rich in gold granules (Fig. 9.35) [2261].

The origin of circumscribed necroses with pseudo-palisades in glioblastoma also have been differently interpreted. It has been proposed, for example, that necrosis of



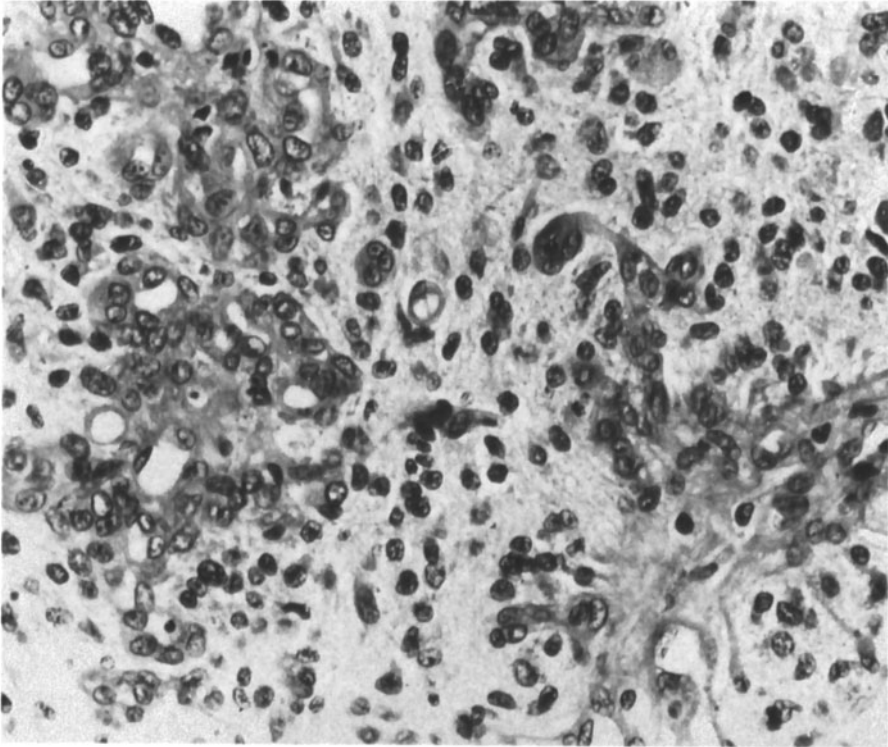
**Fig. 9.32.** Glioblastoma, computer-assisted three-dimensional reconstruction of vessels with endothelial hyperplasia. (From [3030])

the glial cells releases fibroblast growth factor (FGF), a potent mitogenic and angiogenic factor, which stimulates tumor cells and endothelial cells to proliferate, hence the pseudo-palisades and the blood vessel hyperplasia [2583].

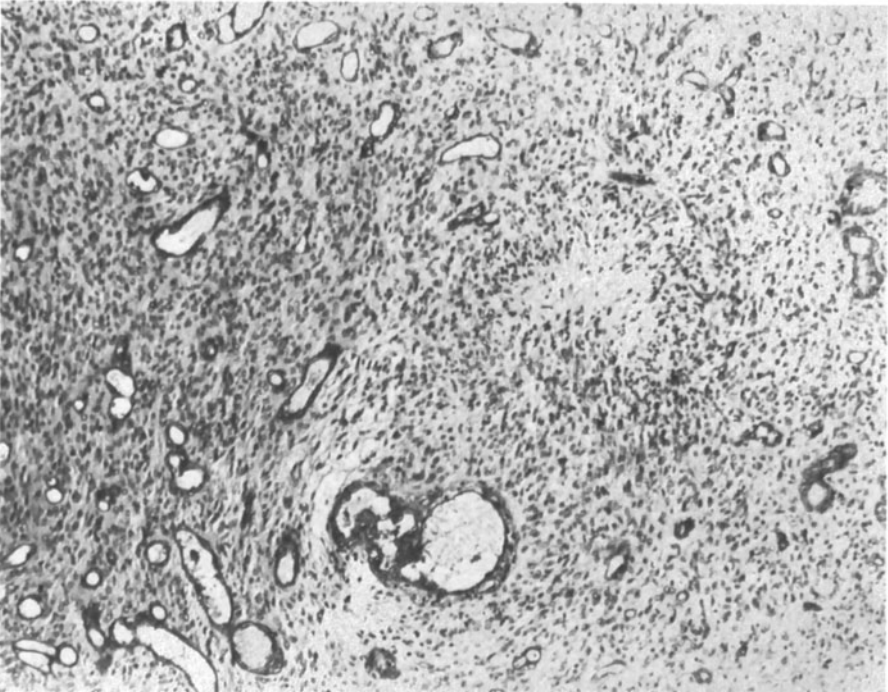
The hypothesis that circumscribed necroses follow the endothelial proliferation and that this follows tumor invasion may be confirmed in the invaded cortex by the observation that if the infiltration proceeds from the white matter towards the cortical surface, the glomeruli will be found in the deep cortical layers (Fig. 9.36); if, on the contrary, the infiltration descends from the subpial region towards the white matter, the glomeruli will be found in the superficial cortical layers [3030]. This sequence derives from the fact that endothelial hyperplasia affects the cortical vascular network, which is formed by the penetrating meningeal branches and their lateral branches [1238, 147].

All the investigations on angiogenesis refer to the hypothesis that all solid tumors are angiogenesis-dependent and that every increase in the tumor cell population has to be preceded by an increase in capillaries which converge on the tumor [923]. Originally, the experimental demonstration that the tumor could induce the formation of new capillaries despite the tumor cells being separated from the vascular bed

**Fig. 9.33a,b.** Glioblastoma. **a** Endothelial sprouts from small vessels in the invaded cerebral cortex. H&E,  $\times 400$ . **b** Circumscribed necroses are found among glomeruli. H&E,  $\times 150$  ▷

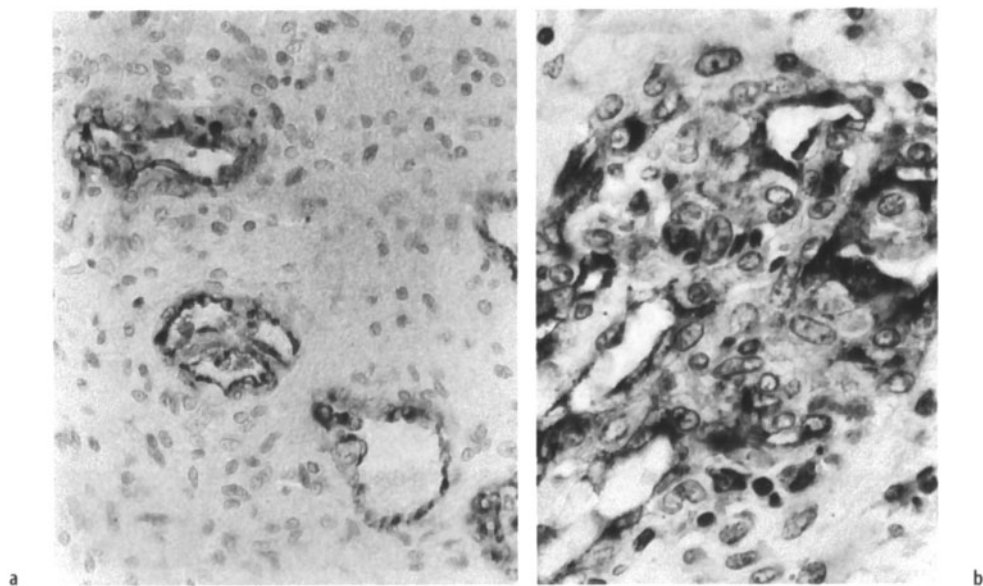


a



b





**Fig. 9.34a,b.** Glioblastoma. **a**  $\alpha$ -sm-actin-positive cells in hyperplastic endothelium. PAP-DAB,  $\times 300$ . **b** Factor VII/RAg is positive only in cells lining the lumen. PAP-DAB,  $\times 400$



**Fig. 9.35.** Glioblastoma. Weibel-Palade bodies in hyperplastic endothelial cells containing factor VII/RAg. Immunogold,  $\times 40\,000$

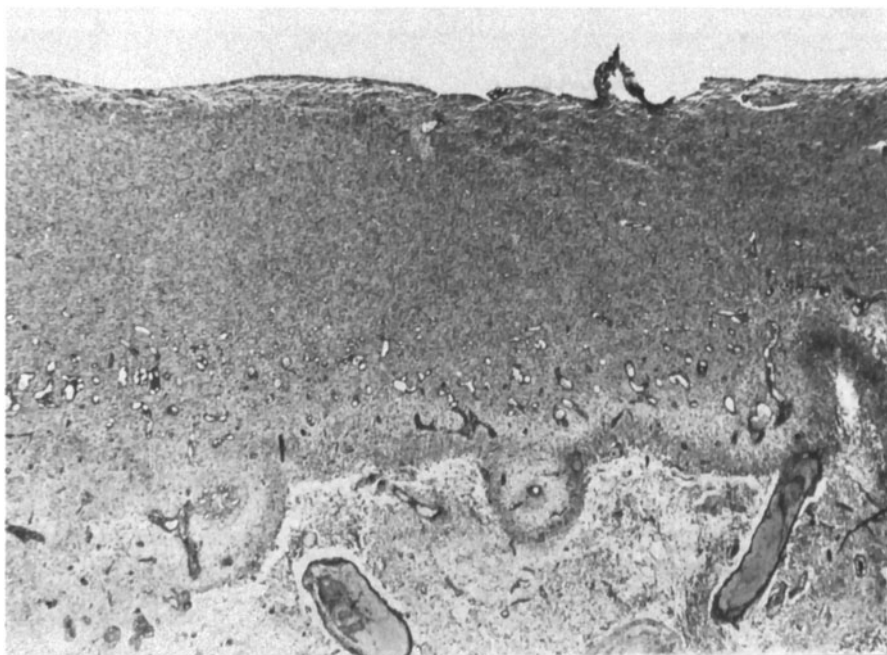


Fig. 9.36. Glioblastoma. Glomeruloid formations in the deep cortical layers, bordering central necrosis. (From [2994]). H&E,  $\times 50$

[1163] led to the supposition that the tumor released a diffusible factor, which was later isolated. Further progress was due to the use of the corneal microchamber in rabbits, the chorion-allantoid membrane in the chick embryo, and in vitro cultures of endothelial cells. The studies were then extended to the enzymatic degradation of the basement membrane, to the locomotion of endothelial cells, and to their proliferation. The enzymatic degradation of basement membranes is accomplished by means of various proteinases. Endothelial cells produce a collagenase which degrades type I collagen and also the type IV collagen of basement membranes [1091]. Substances derived from the retina may stimulate the degradation of type IV collagen, laminin, and fibronectin by endothelial cells. At the same time they stimulate endothelial cells in culture to release plasminogen activator, which converts plasminogen into plasmin, which in turn degrades laminin and fibronectin.

Various angiogenic factors are recognized nowadays [924]. First of all, there are the heparin-binding growth factors for endothelial cells, among which is FGF, derived from the brain, ECGF (endothelial cell growth factor), derived from the eye, and an acid factor derived from the retina. The corresponding receptors have been found in endothelial cells. These factors are found in all tissues. In particular, for FGF, another autocrine stimulation has been proposed [3104]: The endothelial cells express FGF, and as they bear the corresponding receptor, they stimulate themselves to proliferate in an autocrine fashion. FGF has been demonstrated immunohistochemically in endothelial cells in the majority of cerebral tumors [2583], as well as its receptor in hu-

man endothelial cells [2404]. Antibodies against FGF inhibit in vitro the growth of endothelial cells [2919]. This could represent a good therapeutic "hook," but there are no data on cerebral tumors. An autocrine stimulation had already been proposed for PDGF- $\beta$  and for its receptor, both expressed by endothelial cells [1304] (see Chap. 2).

Another factor isolated from a human adenocarcinoma cell line is angiogenin, which has sequence homologies with pancreatic ribonuclease. It is a potent angiogenic factor in the embryonal chorion-allantoid membrane of chick embryo, but its mechanism of action is unknown [892]. There are TGF- $\alpha$  and - $\beta$ , and a series of factors among which those of low molecular weight are mitogenic for the endothelium [883]; others isolated from fluids and from macrophages may stimulate the locomotion, but not the proliferation, of endothelial cells [3703]. Macrophages, prostaglandins PGE<sub>1</sub> and PGE<sub>2</sub>, and a factor isolated from T lymphocytes may be angiogenic. The presence of a renin-angiotensin system in the CNS has been demonstrated and the components localized immunohistochemically [1020], angiotensin II in rat embryonal neurons and renin both in neurons and glial cells [2986]. The small cerebral blood vessels contain receptors for angiotensin II [3278]. The renin-angiotensin system is able to induce angiogenesis [886] through a mechanism well-studied in the ischemic kidney [2589]. In glioblastoma, renin has been demonstrated immunohistochemically in tumor cells, especially around blood vessels, while it has not been found in astrocytoma cells and reactive astrocytes in gliosis [90].

Among the various factors recognized as modulating angiogenesis through a series of mechanisms and associations are heparin and copper [924].

Some angiogenic factors stimulate endothelial locomotion or proliferation or both [924]. Indirect stimulation may occur through macrophages [144, 135] or through the release of endothelial mitogens contained in the extracellular matrix [3558]. The angiogenesis may, however, be regulated by physiological mechanisms which inhibit it. One of these is represented by the contact of the pericytes with endothelial cells [2512] or by the binding of cortisone derivatives with heparin fragments. Some observations in cerebral tumors have been made. If culture medium from human malignant gliomas is added to endothelial cells from human umbilical cord vein in culture, they cause endothelial proliferation [1628]. Similar results were obtained also with well differentiated gliomas [1338]. Using the chick chorion-allantoid membrane model, angiogenic activity has been caused by extracts of glioblastoma, meningioma, and neurinoma [2055]. From personal experience with this method, it is also possible to demonstrate angiogenic activity in carcinoma metastases.

The best demonstration that malignant cells are capable of releasing mitogenic and angiogenic factors is given by their causing endothelial cell proliferation in vitro [1628]. Now widely acknowledged is vascular endothelial cell growth factor (VEGF), 34- to 43-kDa glycoprotein that is mitogenic for endothelial cells [889]. It seems that VEGF is involved not only in angiogenesis, but also in other vascular mechanisms, such as differentiation and repair [2297]. VEGF mRNA in gliomas is located in cells surrounding necroses [2654, 3105]; capillaries are located alongside. In glioblastoma, VEGF receptors are located in endothelial cells [2654, 3105]. VEGF induces an increase in permeability with extravasation of fibrinogen to form a fibrin gel which favors fibroblast and endothelial cell invasion [795]. It has been also designated vascular permeability factor (VPF). A high correlation between the presence of VEGF and the occurrence of peritumoral brain edema in cerebral metastases has been found

[3330]. In vitro, VEGF antibodies reduce tumor growth and vessel density [1674]. In humans, there are four different VEGF isoforms, VEGF-121, -165, -189, -206, arising by alternative splicing of mRNA. VEGF-165 is the most abundant isoform. Several tyrosine kinase receptors have been described. High-affinity receptors FLT1 and KDR are restricted to endothelial cells [1262], but in vitro they are also expressed on other cells [2653]. The location of upregulated VEGF mRNA in cells surrounding necroses in glioblastoma is an intriguing problem. Since VEGF is upregulated in response to hypoxia in vitro [3105, 2654], it has been deduced that palisading cells are hypoxic but not yet necrotic. In fact, they do not stain with Ki-67 [2653]. There is remarkable evidence that VEGF is a major regulator of embryonic angiogenesis.

Among other factors involved in angiogenesis, FGF-1 and -2 must be considered. They first appeared as potent angiogenetic factors [924], but they are also mitogenic for several other cell types. FGFR mRNA has not been found on vessel cells [2653], so that FGF does not seem to play a role in tumor angiogenesis. It has been demonstrated that PDGF receptors are expressed on microvascular endothelial cells [187]. PDGF- $\beta$  receptor is not expressed in vascular cells of normal brain, but in glioblastoma it is up-regulated in vascular cells [2654]; PDGF- $\alpha$  receptor was found in tumor cells, but not on endothelial cells (see Chap. 2). There are two possible mechanisms: autocrine stimulation (tumor cell to tumor cell), involving PDGF AA, AB, BB, and PDGF- $\alpha$  receptor, and paracrine stimulation (tumor cell to vascular cell), involving PDGF AB, BB, and PDGF- $\beta$  receptor. PDGF can also stimulate smooth muscle cells, and this may happen in glomeruli of glioblastoma composed mainly of  $\alpha$ -sm-actin-positive cells [1210, 3651].

### 9.2.2.10

#### *Cellular Kinetics*

As already mentioned in Chap. 7, there are various ways to study cell kinetics in gliomas which do not differ significantly in value and reliability. Generally, both the mitotic index (MI) and the LI obtained with [ $^3\text{H}$ ]thymidine, BrdU, or Ki-67 are lower and more uniform in anaplastic astrocytomas and higher and widely variable in glioblastomas. This means that great morphological and proliferative heterogeneity in malignant gliomas exists and that the different areas of the tumor are not equivalent. For this reason, the principle of not using averages of several measurements but taking the highest labeling value as characteristic of the tumor is widely accepted [2322]. This is especially important in the examination of surgical or stereotactic biopsies, where the quantity of material available is very limited.

### 9.2.2.11

#### *Metabolism*

The level of adenosine triphosphate (ATP) gives a measure of the metabolic efficacy of a tissue, and in malignant astrocytomas the mean ATP and total adenylate levels are higher than in normal tissue [2029, 1416]. Brain tumors utilize more glycolysis than respiration for the production of ATP [3612], continuing lactate production even when oxygen is present. ATP production through glycolysis is anaerobic, and allows growth independent of oxygen provided that a satisfactory supply of glucose is

maintained: Tumors survive ischemia longer than normal tissue [1690, 2563]. As a consequence, the cerebral glucose uptake and consumption by a tumor may be up to three times normal [3255], as demonstrated by using deoxyglucose with PET [1474, 719, 2572, 3476]. Perhaps the reduction of the citric acid cycle and oxidative phosphorylation, due also to the lower number of mitochondria of tumor cells in comparison with normal [1957], accounts for this [2594].

In the glycolytic pathway, a decrease in hexokinase and phosphofructokinase activities in malignant gliomas has been demonstrated [2030, 2139], with normal pyruvate kinase activity and lactate production, due to the depressed citric acid cycle activity. Some enzymes of the glycolytic pathway occur in altered or in more primitive forms.

In the citric acid cycle, citrate synthetase and malate dehydrogenase activities are decreased in tumors with normal succinate dehydrogenase activity [3544, 2030]. Less acetylcoenzyme A (acetyl-CoA) is utilized, and pyruvate accumulates, increasing the level of lactate. Since NADH is not produced, oxidative phosphorylation is depressed. Its associated enzymes are in fact decreased [1957] and cytochrome oxidase activity appears to be inversely related to malignancy [41].

The pentose phosphate pathway, as an alternative pathway, is more active in gliomas, and the glucose-6-phosphate dehydrogenase activity is strongly increased [2030]. Through this pathway, not only is energy in the form of NADPH produced, but also pentose is provided for the synthesis of purines and pyrimidines [2588, 3544].

The synthesis of glycogen in brain tumors is practically absent. Very interesting are the changes in the enzymes of energy metabolism. For example, of the pyruvate kinase isoenzyme subunits, only the fetal type K is produced in glioblastoma [3443] and of the isoenzymes of hexokinase, only the type II [197]. Of the types H and M of lactate dehydrogenase (LDH), only the M subunit is produced in malignant gliomas. The level of isoenzyme LDH5, containing only the M subunit, is greatly increased [1214, 3440, 980].

ATPase and cyclic adenosine monophosphate (cAMP) are inversely correlated with malignancy [1885, 3159]. Of the different cAMP dependent protein kinases, type III occurs in glioblastomas, similar to type II [951], which is activated by cAMP and cGMP. There is in tumors an increased response to cGMP and a decreased response to cAMP. Also, a relationship between malignancy and cAMP phosphodiesterase has been found [950]. From the histoenzymologic point of view, different patterns have been described in gliomas, with various interpretations. Particularly interesting are the strong positive reactions for NADH and NADPH tetrazolium reductase in reactive-type cells and in endothelial cells of vascular proliferations [2996, 2398, 2993].

Acetyl-CoA is the key point in the cell metabolism, being involved in both catabolic and anabolic pathways. In normal nervous tissue, fatty acids are not utilized as a source of energy, and nothing is known about tumors in this regard. The synthesis of fatty acids begins with acetyl-CoA; the synthesis of sterols also begins with acetyl-CoA, and cholesterol is the major sterol in malignant gliomas [1013]. The level of desmosterol, the immediate precursor of cholesterol, is elevated in malignant tumors [3636, 2554] and has been proposed as a marker of tumor activity [2554].

Among many other metabolic properties of gliomas, the increase of the arachidonic acid metabolite thromboxane B must be recalled [452], which is involved in BBB permeability. Other compounds of interest include the polyamines such as putrescine,

spermine, and spermidine, which seem to show higher levels in malignant gliomas [1237, 3562]. For further information, specialized review articles are available [2092].

#### 9.2.2.12

##### *Prognosis and Treatment*

Glioblastomas have, in general, a worse prognosis than anaplastic astrocytomas [3595]. Even if the delimitation between the two oncotypes is sometimes uncertain, they have to be maintained as separate entities. It would not be correct, in designing and evaluating the effects of therapies, to put glioblastoma and anaplastic astrocytoma into one category of so called high grade gliomas. The median survival of adequately treated glioblastomas is 6–12 months, with 8%–12% survivors at 2 years and 5% at 5 years [394, 2401, 2071, 3694].

In spite of this poor prognosis, individual histological parameters may have different predictive significance. Glioblastomas containing microcysts, necroses with pseudo-palisades instead of large necrotic areas, well-differentiated astrocytic cells, or large astrocytomatous areas are associated with longer survival times than those uniformly composed of small cells or cells with small average nuclear size [388]. A better prognosis has also been found to be associated with the presence of calcifications [3380], although an association has been subsequently denied [388]. The presence of giant cells is positively correlated with survival [390]. In general, the giant-tocellular variant has, in fact, a better prognosis when compared with the classic tumor [2108]. The lymphoplasmacellular perivascular infiltrates do not seem to be important in glioblastomas in relation to prognosis [3011, 390, 388], while opposite results have been noted by gathering grades III and IV tumors into a single group [2170, 351, 2914]. The prognostic value of kinetic parameters, such as the LI with [<sup>3</sup>H]thymidine, is controversial [1404, 305], and it also remains to be defined whether or not there are significant correlations with survival and the DNA “pattern” [954, 2323, 1334].

Age and neurological status are the most important prognostic factors: The percentage of survivors at 18 months is 64% for those under 40 years of age, 20% between 40 and 60 years, and 8% over 60 years [480, 3248].

Studies carried out in the CT era demonstrate that in malignant gliomas extensive removals of more than 90% of the tumor are followed, under the same conditions of mortality, by a lower morbidity than incomplete resections [523, 860, 3531], especially when the preoperative neurological conditions were very good. Macroscopically, total removal is associated with longer survival [408, 60, 3694] than simple biopsy. As a consequence, a removal as total as possible should be performed in patients with good neurological conditions and with a reasonable life expectancy; in the opposite case, a simple biopsy should be done for diagnostic confirmation [2553]. However, the prognostic importance of total removal remains to be confirmed in randomized studies [2700]. In recurrences of malignant gliomas after radiochemotherapy with a disease-free interval longer than the median of expected survival, an operation further prolongs an acceptable survival [60, 1248]. As a general rule, a reoperation must be taken into consideration whenever the recurrence is localized and accessible, independently of oncotype, provided that it is not too early.

External radiotherapy is presently the best postoperative treatment. The usual dose to the tumor is 60 Gy; lower doses (50 Gy) are less effective [3595], but higher doses (70 Gy) are not more effective [480]. There is no general agreement on the amount of brain to be included in the target: tumor volume plus 2 cm [1359] or more [1229] outside the external border of enhancement seen on CT. With MRI, it has been demonstrated that tumor cells are present in T2-weighted images in which hyperintense areas are larger than the peritumoral hypointense areas seen with CT [1630]. However, irradiation of the whole brain did not prove to give better results than that of a more limited area [3148]. The likely explanation is that glioblastoma recurs locally before spreading to a distance. Usually, the irradiation is performed with 60 Gy to the volume of enhancement corresponding to the tumor plus 2–3 cm [1907], or a double volume irradiation is performed: 60 Gy to the volume of enhancement and 43–45 Gy to the remainder of the brain. The total dose is given in single daily fractions of 1.8–2.0 Gy. Minimal residual tumor on CT scan after surgery and radiotherapy is a positive prognostic factor [2359, 3715].

The major risk of radiotherapy is delayed radionecrosis. Its clinical incidence with little residual tumor after conventional radiotherapy is 3%–5% [2263, 2116], but it increases in long-term survivors from 3% to 12.5% when survival is prolonged from 18 to 24 months [3249]. Factors of individual hypersensitivity, such as vascular diseases, systemic hypertension, and diabetes, play a predisposing role; however, the risk of delayed brain damage depends mainly on the number of radiation fractions and, therefore, on the fraction dose [2117]. Hypofractionated treatments with few fractions of high-dose expose the patient to a greater risk [2915] and must be avoided in those with a prognosis longer than 6 months.

Until now, attempts to modify the conventional fractionation by increasing the number of daily treatments (hyperfractionation and accelerated fractionation) has not given better results [321, 1870]. Reirradiation at recurrence does not seem to be useful and increases the risk of brain damage [763]. Preoperative radiotherapy, with some exceptions, does not prolong survival and increases morbidity because of vessel fragility at surgery.

New therapeutic modalities such as hypoxic cell radiosensitizers, neutrons, hyperthermia, thiol-depleting agents, halogenate thymidine analogues, boron slow neutron capture therapy, and photodynamic therapy have not proven to be superior to conventional modalities [716, 1282, 1876, 2617, 2926, 3657, 2928].

The tendency of malignant gliomas to recur locally [1359], with the development of multiple lesions in only 5%–9% of cases [510], and the high radioresistance both in vivo [321] and in vitro [2701] allow one to consider interstitial irradiation (brachytherapy, stereotactic radiotherapy) as a possible therapeutic measure. In recurrent tumors, after conventional treatment, both modalities seem to be of some efficacy [1909, 1224, 3155, 3156]; in newly diagnosed tumors, after surgery, they might be employed as a boost to external radiotherapy, but the survival advantage over the external radiotherapy alone is minimal [2002, 3236].

Chemotherapy is of limited value in the treatment of glioblastomas [918]. In the postoperative treatment, BCNU and procarbazine, as single agents administered systemically, in association with radiotherapy, have been demonstrated to slightly increase the percentage of patients with long-term survival over radiotherapy alone. Polichemotherapy with PCV (procarbazine, CCNU, and vincristine) seems to be

superior to BCNU alone [1929]. Intra-arterial chemotherapy, employing nitrosoureas (BCNU, PCNU, ACNU, HeCNU) or platinum compounds (cisplatin, carboplatin) does not improve survival over conventional systemic chemotherapy (BCNU) and carries a high risk of retinal damage and leukoencephalopathy [764, 3149, 2928].

In the treatment of recurrent tumors after conventional therapies, BCNU, CCNU, and procarbazine remain the most effective single agents; other drugs such as cisplatin, carboplatin, dibromodulcitol, tamoxifen, and lonidamine have shown some activity. Me-CCNU, hydroxyurea, podophyllotoxins (VM 26, VP 16), bleomycin, dacarbazine (DTIC), 5-fluorouracil, and methotrexate are ineffective. New drugs such as topotecan, taxol, temozolamide, phenylacetate, and thalidomide are under investigation [621, 1177, 2678, 3769]. Of the drug combinations, PCV (CCNU, procarbazine, and vincristine), cispatin-VP 16, and carboplatin-VP 16 are the most commonly employed. High-dose systemic chemotherapy with bone marrow or stem cell rescue or in association with hematopoietic growth factors (granulocyte colony-stimulating factor, G-CSF, granulocyte-macrophage CSF, GM-CSF) is undergoing investigation. Intra-arterial chemotherapy has no advantages. Interstitial chemotherapy with a controlled delivery of drugs (BCNU, taxol, camptothecin) by biodegradable polymers [328] and new forms of immunotherapy [2803, 253] and gene therapy [2928] are under investigation.

Glioblastoma metastasizes extracranially to the lungs, lymph nodes, pleura, liver, etc., almost exclusively in patients who have undergone brain surgery. The occurrence of extracranial metastases in the absence of surgery is very rare; just over ten cases have been reported [1911].

### 9.2.3

#### Gliomatosis Cerebri

The term “gliomatosis cerebri” was used to indicate a diffuse increase in glial cells found in large areas of the brain with a poor tendency to grow as a discrete tumor [2418]. These cases were assimilated to others previously described as “gliomatosis” [1320], diffuse glioma [1856], the blastomatous type of diffuse sclerosis [449], diffuse systematic blastomatous growth of the glial apparatus [3099], diffuse cerebral schwannosis [919], diffuse central lemmoblastosis [3575], “glioblastosis diffusa” [3630], etc. Recently, ten new cases with a review of 48 others from the literature have been reported [100].

The diagnosis of the disease is not usually made clinically. There is a progressive cerebral syndrome with intracranial hypertension, even if cases with acute onset are not lacking. The duration of the illness is very variable and may be up to 20 years. Even from the radiological point of view, its recognition is very difficult. By CT scanning, the lesion appears as iso- or hypodense, even after contrast enhancement. Sometimes the only finding on CT may be the swelling of parts of the brain. If necroses or hemorrhages appear, these can be seen but not attributed to the disease [100]. MRI is now the resolute imaging modality [2848].

Macroscopically, the brain is slightly enlarged, but it maintains its normal shape.

Histologically, there is a diffuse proliferation of glial cells in the white matter, with a prevalent “spongioblastic” elongated character and a possibly polymorphous aspect (Fig. 9.37). Mixed areas and also foci of undifferentiation up to a glioblastomatous appearance may be present. The cells are variably GFAP positive.



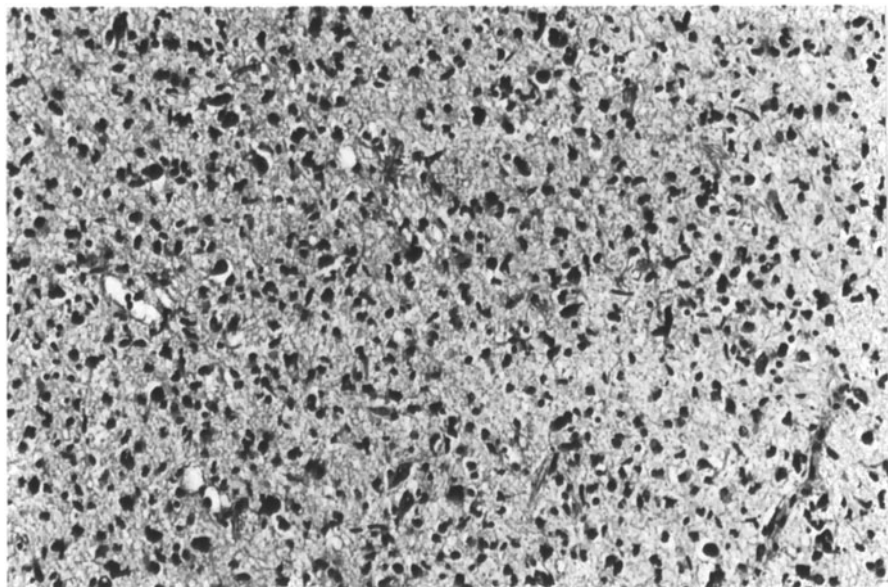


Fig. 9.37. Gliomatosis cerebri, diffuse astrocytic proliferation. H&E,  $\times 200$

Apart from the hemispheres, the brain stem, cerebellum, and spinal cord may also be involved. A case in which the main localization was spinal has been reported; besides astrocytes, there was a diffuse microglial component [2422] which is difficult to interpret unless a neuroectodermal origin for microglia is accepted. This remains, however, a widely discussed topic.

The differential diagnosis includes multicentric and mixed gliomas.

#### 9.2.4

##### **Pleomorphic Xanthoastrocytoma**

This is a neoplasm affecting almost exclusively infants and adolescents with a peak incidence in patients between 10 and 20 years old [1649, 1650, 1803, 2920, 2080, 3327, 3641, 1130, 2076, 2546, 2565, 1153].

The tumor is located supratentorially, mostly in the temporal lobe. Infratentorial and extraparenchymal extensions are exceptional [2565], as is infiltration of the brain stem [3327].

#### 9.2.4.1

##### ***Macroscopic Appearance***

The tumor is superficially located with involvement of the leptomeninges and sparing of the dura, even if there is erosion of the skull bone [1650, 2080]. A cystic component containing xanthochromic fluid may be present, and the tumor can be confined to a yellowish mural nodule. Rarely, necrosis is present [1650, 2080].

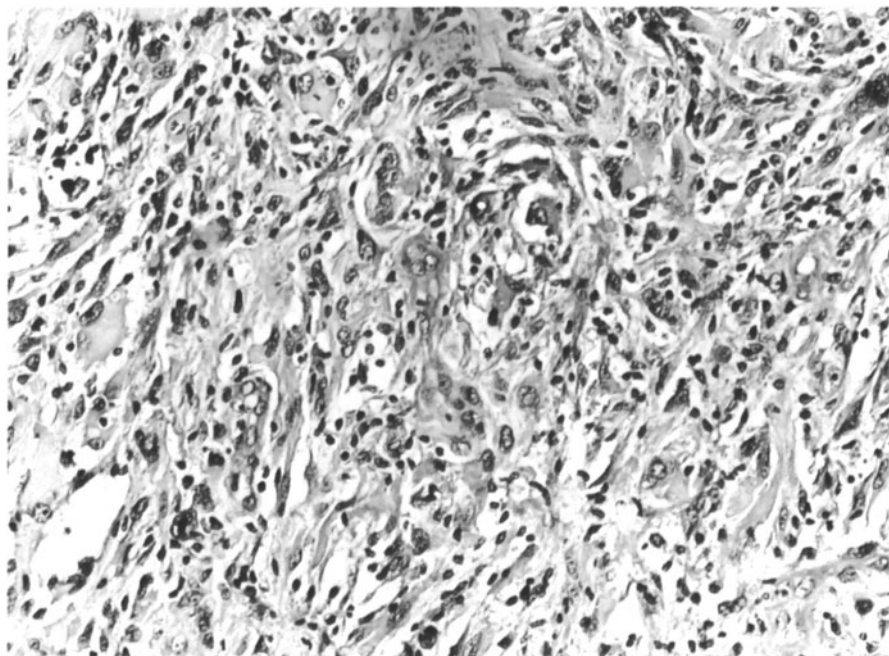


Fig. 9.38. Xanthoastrocytoma; spindle cells admixed with xanthomatous cells. H&E,  $\times 400$

Clinically, the tumor is associated often with epileptic seizures. CT and MRI show frequently a cystic tumor with enhancement after gadolinium.

#### 9.2.4.2

##### *Microscopic Appearance*

The neoplasm, which seems to originate from subpial astrocytes [1644], extends into the leptomeninges and invades the cortex both directly and along the Virchow–Robin spaces. It features a polymorphous proliferation with a moderate cellular density and a mostly fascicular pattern of growth (Fig. 9.38). The stroma is formed by an abundant reticulin network which surrounds single elements or small groups of cells. There is no particular reticulin thickening around the blood vessels, which are not significantly increased in number and do not show endothelial proliferation.

The cell composition is polymorphous. Beside fusiform cells with oval nuclei, there are large, often giant, roundish or polygonal ones with microvacuolar (xanthomatous) cytoplasm with a thin peripheral eosinophilic rim which may be GFAP positive (Fig. 9.39). Some cells contain periodic acid-Schiff (PAS)-positive cytoplasmic globules while others are large with giant, sometimes multiple and bizarre nuclei. There are no necrotic areas, and mitoses are rare or absent.

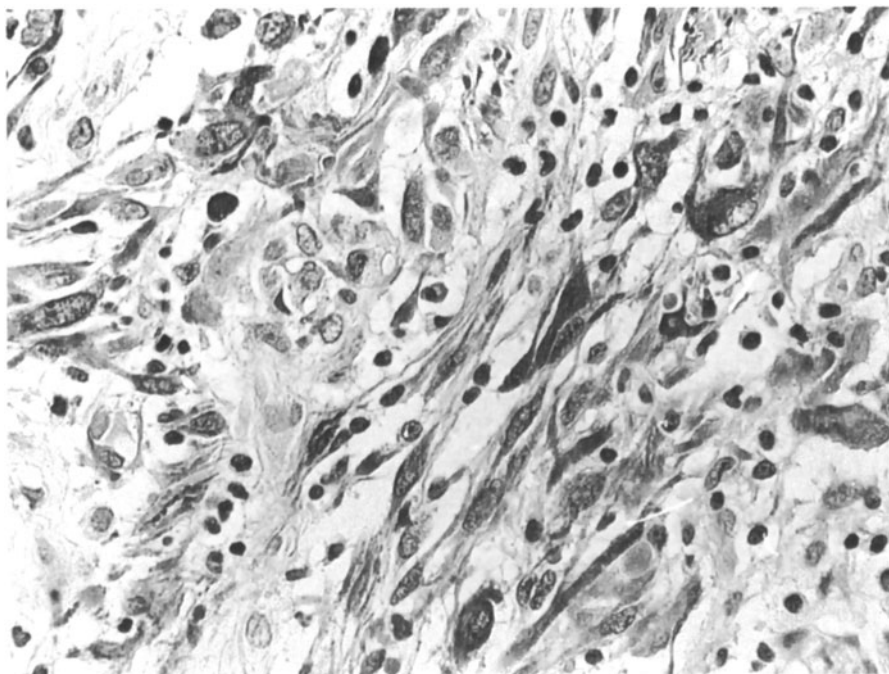


Fig. 9.39. Xanthoastrocytoma; large, glial fibrillary acidic protein (GFAP)-positive astrocytes. PAP-DAB,  $\times 400$

Perivascular lymphoplasmacellular infiltrates are constantly present, with the exceptional formation of lymphoid follicles [1650]. Rarely, mast cells are also seen [2565].

GFAP is variably present [668, 1130, 1650, 1803, 2080, 2546, 2565, 2920, 3327, 3641]. It is often absent in fusiform cells including those that apparently aid the infiltration of the neoplasm along the Virchow–Robin spaces. The majority of cells are strongly vimentin positive. The abundance of reticulin is due to the involvement of the leptomeninges and to the presence of basement membranes around subpial astrocytes, seen under the electron microscope, produced by the astrocytes themselves and not by the pial cells [2726, 2621]. It is known that the capacity of nervous tissue to synthesize collagen begins during embryogenesis and that it is at times maintained by glial cells in adult life [546].

$\alpha_1$ -Antichymotrypsin may be present in the cytoplasm of some reactive histiocytic cells, likely of subarachnoid origin [2080, 2076]. It may be coexpressed with GFAP or vimentin in the same cell, possibly indicating that glial cells acquired phagocytic activity. Ultrastructural investigations [1650, 1803, 2080, 2565, 3641] have demonstrated that besides masses of 8- to 10-nm filaments, lipopigment granules and microtubules occur in the cytoplasm of tumor cells.

The nosographic problem of this tumor is essentially that of its relationship with leptomeningeal fibroxanthoma [1648]. GFAP expression may, in fact, be limited to a few cells and may be absent in the meningeal neoplasm [2577]. It could also be the

result of a process of phagocytosis or endocytosis. According to some authors, the tumor is considered a fibroxanthoma of the meninges [2577], in agreement with the original interpretation [1648].

The fact that malignant evolution of the tumor is toward glioblastoma and not sarcoma seems to indicate a glial nature [1657]. Another nosographic uncertainty concerns ganglioglioma. Mixed cases have been reported. In one xanthoastrocytoma, the tumor formed the astrocytomatous component of a ganglioglioma [1003]; in another patient, it was a component of a cerebellar ganglioglioma [1967]. A case with a gangliomatous component has also been described [1751].

Two cases have been reported with prominent vascularity and desmoplastic changes, and the existence of an angiomatous variant has been suggested [3337].

### 9.2.4.3

#### *Prognosis*

The tumor has a relatively good prognosis [1650, 1803, 3327, 1130, 2546, 2565], with long survival periods (up to 25 years), although cases of rapidly fatal evolution have been reported [3641, 2565, 1657].

Anaplastic changes in glial cells have been observed [643, 3641], including in one of our cases after radiotherapy. In eight primary and recurrent cases of this tumor type, the DNA was analyzed and the findings suggested that the genetic events that accompany the tumor formation and progression may differ from those in diffuse astrocytoma tumorigenesis [2587].

The superficial location allows an easy surgical approach. Recurrences have been described in some cases [1650, 1803, 3327, 3641, 1130] with morphological modifications towards malignancy, such as the appearance of necroses, thus justifying the name of malignant glioma or glioblastoma.

The differential diagnosis must include fibrohistiocytomas (xanthomas) and “desmoplastic” glioblastoma [464] of the meninges or brain [1648, 1847, 38, 1576, 3202] and atypical meningiomas or meningeal sarcomas [1803, 2080, 3327]. GFAP positivity may be helpful in the distinction.

### 9.2.5

#### **Subependymal Giant Cell Astrocytoma (Tuberous Sclerosis)**

The subependymal region is one of the sites at which the hamartomatous lesions of tuberous sclerosis may become manifest. The others include the kidney, lung, and heart. Apart from the cerebral cortex tubers, nodular, smooth, pinkish, “candle guttering” masses arise from the surface of the lateral ventricles (Fig. 9.40), especially in the frontal horns. They can grow to a large size and obstruct the foramina of Monro, are sometimes calcified, and can also appear in subjects in whom tuberous sclerosis is not suspected. It must be stressed, however, that in the Mayo Clinic series of the 345 patients with tuberous sclerosis complex, 20 were identified as having subependymal giant cell astrocytoma. No example of this tumor without features of tuberous sclerosis was found [3158]. Maybe this is due to the

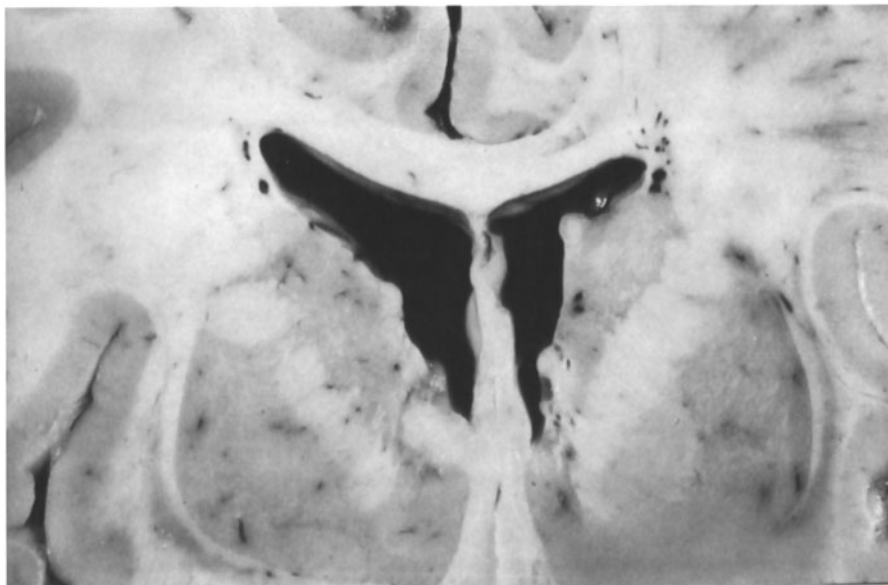
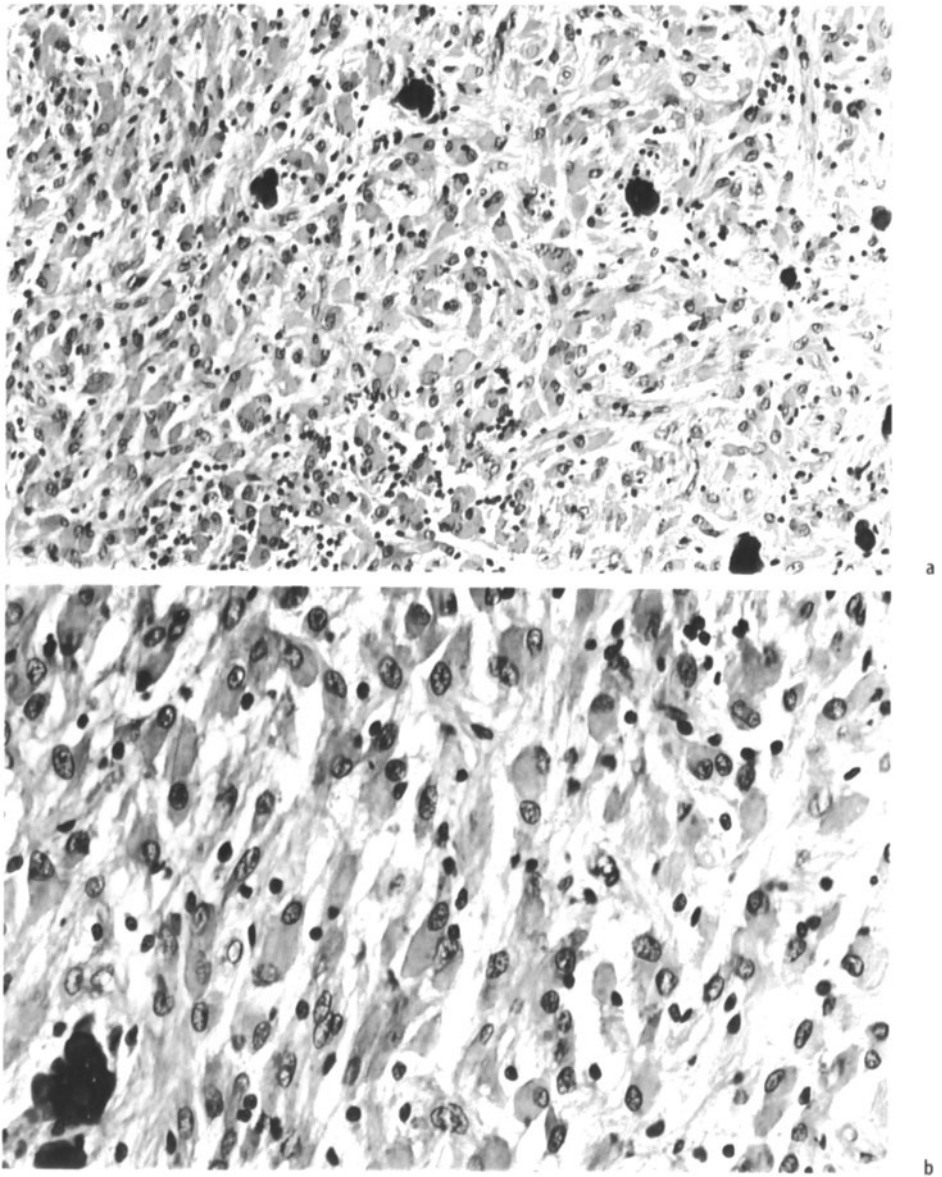


Fig. 9.40. Tuberous sclerosis, “candle guttering” masses on the ventricular wall

investigations being carried out in pre-MRI era. Usually, individuals under the age of 20 years are affected. About 20 newborns less than 1 week old affected by tuberous sclerosis have been described [2519], and in three of these, subependymal tumors were present.

The tumor is composed of giant astrocytes with eosinophilic cytoplasm, sometimes elongated in shape, gathered in bundles with clearly evident processes (Fig. 9.41). Nuclear polymorphism is marked, but mitoses are rather rare. The differential diagnosis includes gemistocytic astrocytoma, which is usually situated in the white matter and affects older subjects. The absence of features of malignancy, such as circumscribed necroses and marked mitotic activity, distinguishes this tumor from glioblastoma.

In the older literature, mention is made of the possibility that at least part of these cells with ganglionic appearance are neuronal in origin [1098]. In two cases, in fact, it has been observed that the large cells were GFAP negative but neuronal-specific enolase (NSE) positive [3293]. In other reports, GFAP positivity was limited to the peripheral part of the cytoplasm and absent in the processes [785], present only in a certain percentage of cells [3533], or even completely absent [2390]. In a series of 22 cases, it was found that GFAP is constantly present in a variable number of cells in tumors not associated with the tuberous sclerosis complex. In tuberous sclerosis-associated tumors, in contrast, GFAP-positive cells are scarce or absent. Positivity for the 68-kDa neurofilament (NF) subunit has been observed in six and for NSE in 13 out of 18 patients [302]. Because there do not seem to be any doubts about the glial nature of the tumor, it can be concluded that the GFAP-negative cells are incapable of producing such proteins.



**Fig. 9.41a,b.** Subependymal giant cell astrocytoma; spindle cells and calcifications. H&E, **a**  $\times 200$ , **b**  $\times 400$

Immunoreactivity was also observed for phosphorylated neurofilaments, class III  $\beta$ -tubulin, calbindin, somatostatin, metenkephalin, 5-hydroxy tryptamine, and neuropeptide Y [2979].

There might be dysgenetic cells whose dysplastic nature is responsible for the positivity for neurofilaments. There is, therefore, a bidirectional differentiation which

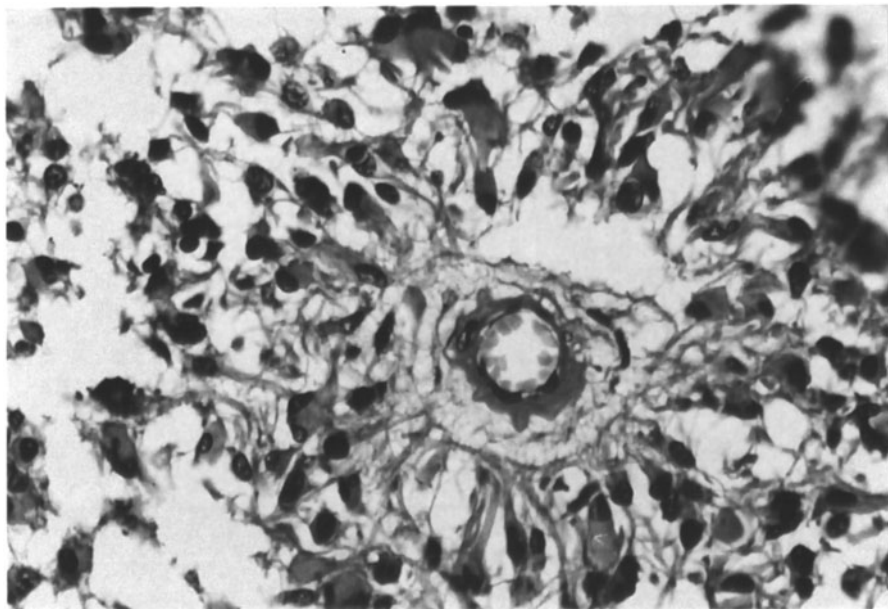


Fig. 9.42. Astroblastoma, tumor cells with processes converging on a vessel. H&E,  $\times 300$

never completely reaches full neuronal expression. Even in a case of a subependymal tumor in a premature infant, tumor cells were either positive or negative for GFAP and positive for neurofilaments, in line with a dysplastic origin [509].

The significance of the positivity for NSE is very doubtful. This marker may be positive in frankly glial cells [3551].

Dense core vesicles, similar to those found in ganglioneuroma and ganglioglioma [2809, 2879], even in the glial component [2879], have been found by electron microscopy [3193]. In only one case were eosinophilic neurosecretory granules seen [2390].

Rosenthal's fibers are present [3046, 3193, 2904].

The necessity of surgical removal is debated [989]; however, it leads to long-term survival without recurrence.

#### 9.2.6

##### Astroblastoma

This is an extremely controversial tumor, accepted by some as an entity and denied by others. It has been described in the cerebral hemispheres and in the paraventricular region in the first decades of life. The tumor "ought" to be characterized by a paraventricular astrocytic arrangement with convergence of broad cellular processes on the blood vessels on which they terminate (Fig. 9.42). In reality, this feature is found both in astrocytomas and glioblastomas. In fact, in the first description of this oncotype two forms, one well differentiated and one clearly malignant, were described [130]. Recognized as an oncotype per se [127], midway between protoplasmatic astrocytoma

and glioblastoma, it has subsequently been considered as a stage in the process of dedifferentiation [1661], as a subgroup of astrocytomas characterized by large cells producing glial fibers [3799], and lastly as an oncotype per se again, even if rare [2904]. There are not many recent descriptions [828, 3533, 1797, 1439, 1352, 2904].

Macroscopically, the tumor is well circumscribed, gray-pink, and sometimes cystic or with central necrosis.

Microscopically, its main feature is perivascular pseudorosettes with cells giving off processes which terminate with their end feet on blood vessels. The processes on the vessels are not the only ones, because others, more or less developed, may be seen. The intervacular cells show the same features. Nuclei may be polymorphous and mitoses present. Sometimes the blood vessels, with thickened and hyalinized walls, contribute to the architecture of the tumor and show only modest and inconstant endothelial hyperplasia. There is often a diffuse papillary appearance.

GFAP staining may be positive but with great variability, especially in the processes reaching the blood vessels.

A benign subtype with few mitoses and no endothelial proliferations and a malignant type with many mitoses and endothelial proliferations have been distinguished. Areas of necrosis and intermediate forms could be present in both types [299]. The differential diagnosis includes especially ependymoma. It is not the expression of GFAP which helps in this respect, because this may be expressed in radial crowns of ependymoma, more so than in the pseudorosettes of astroblastoma, but rather the perivascular processes with end feet which are characteristic of astroblastoma.

Only a few electron microscopy reports are available [1797, 1439, 1352]. The cells may resemble astrocytes, with various degrees of differentiation and numerous filaments. Rosenthal's fibers may be found. In two cases, characteristics intermediate between those of astrocytes (such as the production of glial fibers) and of ependymocytes (such as the development of microvilli on the free surface of the cells), the presence of intercellular junctions, occasional cilia, and interdigitations on the lateral border of the tumor cells, have been described [2880]. These characteristics bring the cells of astroblastoma close to the tanocytes and support the hypothesis that astroblastoma derives from the proliferation of tanocytes [2904] or ependymal astrocytes.

These data indicate, on the one hand, the origin of the tumor, consistent with its occasional paraventricular location, but on the other, they render its nosological limits less distinct. It must be said that electron microscopy has contributed more than immunohistochemistry to the nosographic definition of the tumor.

The biological behavior of astroblastoma seems to be correlated with its histological aspect. Cases with histological features of a well-differentiated glioma have a more favorable prognosis than anaplastic tumors, although the latter may have long survival periods [299].

## 9.3

### Astrocytic Tumors of the Midline

This is a controversial chapter, both from the point of view of the histological classification and of the general nosology. If site (midline) and cellular features (elongated cells resembling the spongioblasts of cytogenesis) have allowed some authors [3799]



to gather these tumors in the spongioblastoma group, it is also true that the majority, but not all, of these tumors are pilocytic astrocytomas [823].

When Bailey and Cushing (1926) [133] replaced the term spongioblastoma by glioblastoma, the former remained to indicate a group of benign tumors characterized by a typical histological appearance and by a location in the optic nerve, chiasm, and hypothalamus [2861, 1393], which were then included in the group of piloid astrocytomas [823]. The studies supporting the definition of spongioblastomas as typical tumors of the dorsolateral prechordal leaflet have already been recounted. They are located in the dorsal and basal part of the neural tube: the spinal cord, medulla, pons, quadrigeminal plate, cerebellum, thalamus, hypothalamus, chiasm, and optic nerve.

### 9.3.1

#### Astrocytoma of the Optic Nerve

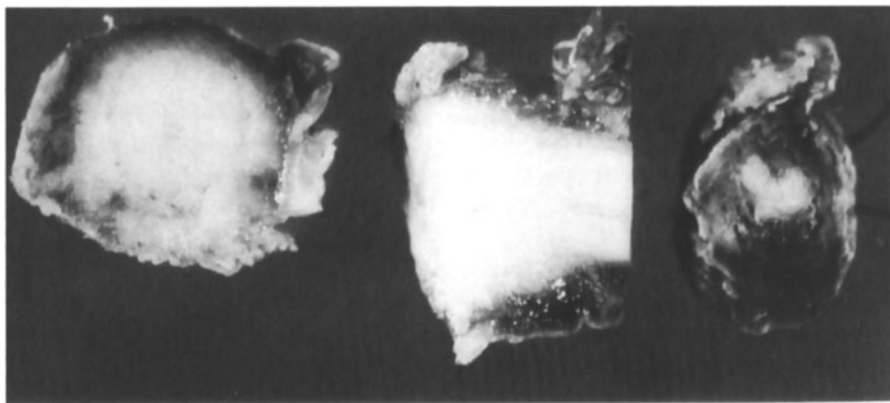
Clinically, the tumor causes a gradual loss of vision. With imaging, a diffuse enlargement of the optic nerve is demonstrable.

Astrocytoma of the optic nerve is typically a tumor of infancy, with an average age at diagnosis of 8 years [740] or even less (3 and 1.5 years) [310], sometimes occurring in cases of von Recklinghausen's disease. The tumor grows within the optic nerve sheath, thereby causing a fusiform dilatation of the nerve (Fig. 9.43a). This is easily visible on transverse section where the nerve seems hypertrophic with evident septa (Fig. 9.43b).

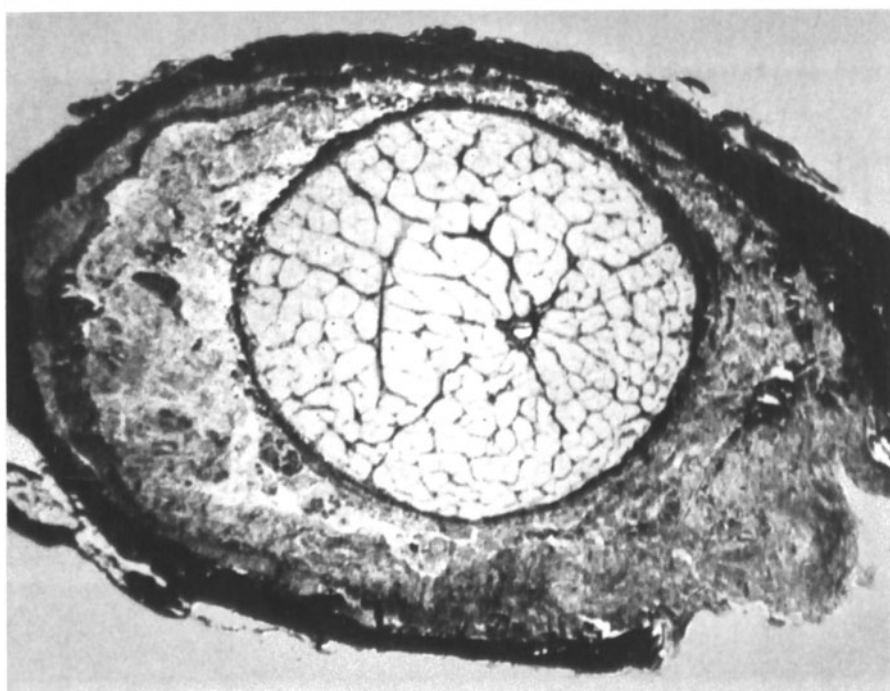
The histological appearance is characterized by bundles of elongated cells producing fibers and oriented along the major axis of the nerve. The bundles are separated by the septa of the nerve (Fig. 9.43b), in which small and medium caliber blood vessels are found. The nuclei are also elongated and moderately polymorphous. There may be abundant Rosenthal's fibers. There is another histological aspect, characterized by a low cell density, loss of the bipolar appearance of the cells, the formation of microcysts, and the widespread presence of mucoid material.

Outside the tumor, there is usually a strong fibroblastic meningeal response which mingles with pilocytic tumor cells (Fig. 9.44). A strong fibroblastic response may also be found in the septa. The tumor is benign and is associated with long survival [310, 3410] if it does not involve the optic chiasm.

After apparently total removal, local recurrence is infrequent [55, Hoffman et al. 2384], and 85% of patients have a mean survival of 17 years [2894]. The merit of postoperative radiotherapy is therefore controversial, but it is usually carried out in cases of incomplete resection [3638, 55, 916, 1765]. It has also to be taken into account that in the adult there is a rare, anaplastic variety with a clearly worse prognosis [1421, 1239] which can come to resemble the picture of glioblastoma [2168]. Up to now, about 30 cases have been described [3390]. Cases with a malignant course have recently been reported also in infancy [3692, 1567]. When the tumor occurs with neurofibromatosis, it is commonly bilateral and has a worse prognosis.



a



b

Fig. 9.43a,b. Optic glioma. a The nerve appears to be hypertrophied. b Fiber bundles are separated by the nerve septa. H&E,  $\times 1$

### 9.3.2

#### Astrocytoma of the Chiasm

Clinically, the patient shows visual loss and changes in the visual field. By imaging, an enlargement of the chiasm can be seen.

As compared with the optic nerve form, astrocytoma of the chiasm affects older children aged 6–14 years [740, 310]. The tumor may extend to the optic nerve or the

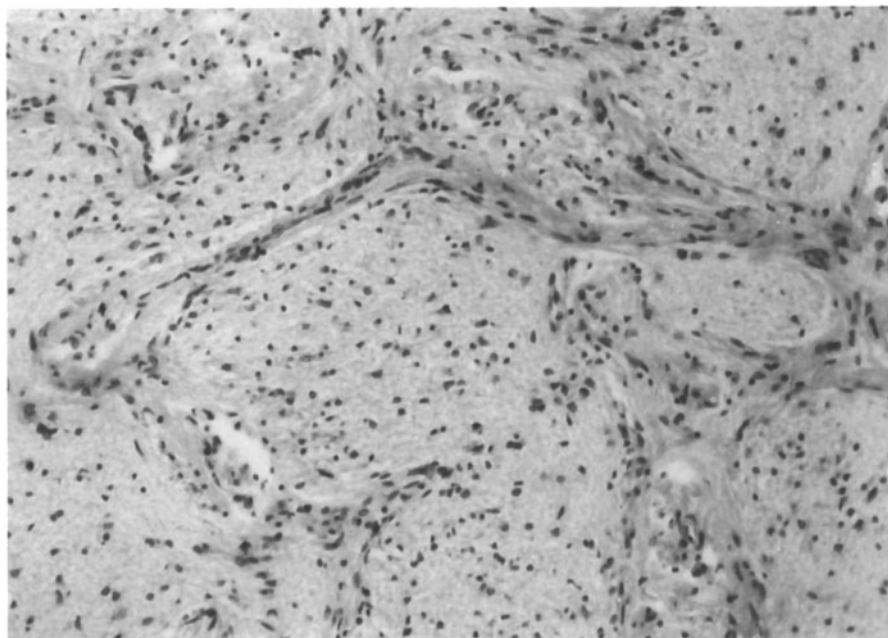


Fig. 9.44. Optic glioma, pilocytic aspect. H&E,  $\times 200$

optic tract, and it may shift or invade the third ventricle and infiltrate the hypothalamus. It may be cystic or hemorrhagic.

Histologically, it is similar to the optic nerve form but for the presence of septa. Rosenthal's fibers may be abundant. There may be endothelial hyperplasia in the small blood vessels.

Even if the anaplastic variety is rare [3692], according to some the prognosis is clearly worse than in the optic nerve counterpart, and only 50% of patients are alive 15 years after operation [310]. It seems that the risk of dying is higher in the first decade after diagnosis [2894, 1459]. The risk of spinal metastasis is practically only theoretical [1734].

The standard therapy is irradiation, even though a full radiobiological rationale is lacking except for those tumors showing anaplastic features. A stabilization of the disease can be obtained [3410, 3713, 1765], but not without deleterious long-term sequelae. Surgery is of limited help, but recently a radical subtotal resection of exophytic growths has been proposed [3702].

Development of anaplastic changes after radiotherapy has been described in optic and chiasmatic astrocytomas [737].



Fig. 9.45. Glioma of the pons

### 9.3.3

#### Brain Stem Astrocytomas

Brain stem astrocytomas occur preferentially in children: 59% of patients are below 20 years of age [2098]. The average age for the infantile form is around 7 years [3446, 31]. The most frequent location is in the pons, followed by the medulla oblongata and mesencephalon. Sometimes the tumor does not form a mass but grows diffusely, giving the anatomical structure a “hypertrophic” appearance (Fig. 9.45); however, it does not usually remain confined to the anatomical structures, extending into the cisterns and through the cerebellar peduncles into the cerebellum (Fig. 9.46) and the fourth ventricle, or it forms small masses on the surface. It shifts surrounding structures and may even encase the basilar artery.

Clinically, the symptomatology depends on the location. Thalamic tumors may cause contralateral sensory loss, hemiparesis, cognitive impairment and visual defects. Pontine gliomas cause cranial nerve palsies, contralateral pyramidal signs, and sensory loss. In the pineal region, typical symptoms with Parinaud’s syndrome and light accommodation reflex disturbances occur. In all these locations, an obstructive hydrocephalus may arise. By imaging, an enlargement of the structures can be seen.

The tumor has a hard consistency and is whitish, but hemorrhage and necroses may be present.

Histologically, most tumors are of the fibrillary type, but the general aspect is often modified by the influence of compact, preexistent structures. In particular, the growth along the long fiber tracts gives the cells an elongated shape. The frankly pilocytic variant accounts for 10%–15% of brain stem tumors [400].



Fig. 9.46. Glioma of the pons extending into the cerebellar peduncle

The tumor very often undergoes malignant transformation, with the appearance of necroses, endothelial proliferation, and invasiveness, and takes the aspect of an anaplastic astrocytoma or even of a glioblastoma.

The rapid invasiveness of the tumor is due to its malignant transformation, but the tumor remains localized and never reaches the cerebral hemispheres [2098]. Contradictory observations have instead been made on its diffusion into the subarachnoid spaces [2437], which could be very important from the therapeutic standpoint.

An investigation by means of multivariate analysis of the correlation between histological features and survival [31] has demonstrated that the presence of mitoses is a clearly unfavorable prognostic sign, while that of calcifications or of Rosenthal's fibers is favorable.

The tumors which are an expression of neurofibromatosis usually carry a more favorable prognosis [2278].

It is clear that these tumors cannot be surgically removed. Operation is generally limited to the removal of the exophytic parts of the neoplasia or to biopsy. It is very important to take into account the marked discrepancy which may exist between biopsy and autopsy diagnosis, the latter revealing a higher proportion of malignant tumors [3446]. This may be due to the poor sampling of the tissue in biopsies and possibly also to the malignant transformation which occurs in the interval between biopsy and death.

The elective therapy is irradiation. Without it, the 1-year survival is only 25%, while with irradiation it is 45% [3547]. In general, the reported survival is poor [31,

1535]; however, recently a 5-year survival rate of 59% was observed after hyperfractionated radiotherapy [1972].

The problem of establishing a prognosis is in relation to the debated question of the usefulness of a biopsy. In this regard, it has to be noted that, in general, patients with a biopsy-proven malignant tumor survive no more than 16 months, whereas those with a benign tumor have an actuarial survival time of 5 years [1986].

Like most gliomas, these tumors are usually markedly heterogeneous, so that the biopsy has maximum reliability only when glioblastoma is detected [837]. For this reason, some authors have questioned the usefulness of a biopsy, especially considering that statistical correlative studies have demonstrated that some clinical signs and CT findings, for example, heterogeneous density, allow one to establish malignancy and predict survival in relation to surgical and radiation therapy [3326, 1864]. A small group of tumors (16 out of 144) characterized by a dorsal exophytic growth into the fourth ventricle, with a benign histological appearance and a good prognosis and a median survival of 7 years, has been identified [1364].

#### 9.3.4

##### **Other Midline Astrocytomas**

Other midline astrocytomas are, on the whole, tumors arising from the walls of the third ventricle, hypothalamus, etc. The histological features are similar to those already described. They are usually benign and most common in infants. Rarely, they may undergo malignant transformation [2437]. Cases of hypothalamic astrocytoma with subarachnoid diffusion have been described [2465, 2084]. For details on therapy, see Sect. 9.3.2.

Astrocytomas may arise in the neurohypophysis. They are very rare and of pilocytic aspect. Once they have reached a certain size, their starting point is no longer recognizable. They are very easily confused with astrocytomas of the third ventricle.

Clinically, hypothalamic gliomas may cause a syndrome characterized by emaciation, hyperactivity, precocious puberty, and hypotension.

#### 9.3.5

##### **Cerebellar Astrocytomas**

##### 9.3.5.1

##### *Nosographic Considerations*

The definition of this oncotype has been debated for a long time. That the cerebellum is a frequent location of astrocytoma was known to Bailey and Cushing [133], but only later did Cushing [625] recognize the cerebellar astrocytoma as a benign tumor of the midline with a high frequency in the juvenile age group. Bergstrand [204] at first considered it an astrocytoma and, given the resemblance of its cell elements to embryonal glia, proposed the term “embryonal gliocytoma.” Later, thought to originate from a congenital malformation, it was denominated “glioneuroblastoma” [205]. In the nomenclature of Elvidge [823] the tumor was placed in the piloid variant

of astrocytoma, and in that of Bucy and Gustafson [369] it was considered as an astrocytoma, with its fibrillary and protoplasmic variants.

Zülch [3796] regarded the tumor as belonging to the spongioblastoma group on the basis of the above considerations, and so did Henschen [1297]. Ringertz and Nordenstam [2795] also regarded the cerebellar astrocytoma as a polar spongioblastoma; however, six cases from their collection showed structures indistinguishable from those of cerebral astrocytoma. On the other hand, according to Ringertz [2794], polar spongioblastoma could occur in 11% of hemispheric cerebral astrocytomas. Russell and Rubinstein [2899–2903] considered cerebellar astrocytomas to be partly pilocytic astrocytomas of the “juvenile” type and partly diffuse astrocytomas.

### 9.3.5.2

#### *Frequency, Age*

It is a frequent tumor, representing 4.7% [660], 6.4% [2994], or 10.1% [2795] of all gliomas. In the present series, it represents 3.2% of all intracranial tumors. In the posterior fossa, it is almost as frequent as medulloblastoma [589, 2994].

It affects adolescents: about 60% are found in subjects less than 16 years old [2994]. The peak of the distribution curve for age is between 5 and 10 years according to Zülch [3799], and between 11 and 20 years according to personal experience. However, cases are also known in the sixth, seventh, and eighth decades of life [1111, 1453, 1454, 1658].

### 9.3.5.3

#### *Macroscopic Appearance*

The tumor has a grayish-yellow color, is soft in consistency, and is often cystic (Fig. 9.47). Sometimes it forms a large cystic cavity with a mural nodule. It can be located both in the cerebellar vermis and, more often, in the hemispheres, where cyst formation is more frequent [1111]. The tumor may invade the fourth ventricle and extend towards the quadrigeminal plate, the cervical spinal cord, or the cerebello-pontine angle.

### 9.3.5.4

#### *Microscopic Appearance*

The cellular density is medium in nondegenerated areas. The cells are elongated, mono- or bipolar, with roundish or oval, clear nuclei, and send out long processes which group into compact bundles that are denser around the blood vessels (Fig. 9.48a). Mitoses are not usually encountered. The nuclei have a thin membrane, are clear, and contain isolated, easily distinguishable chromocenters and nucleoli.

Different aspects may be concurrently present. The appearance may be looser, with vacuolar or mucoid degenerative phenomena which lead to the formation of cysts of various size, often confluent and sometimes filled with an eosinophilic fluid

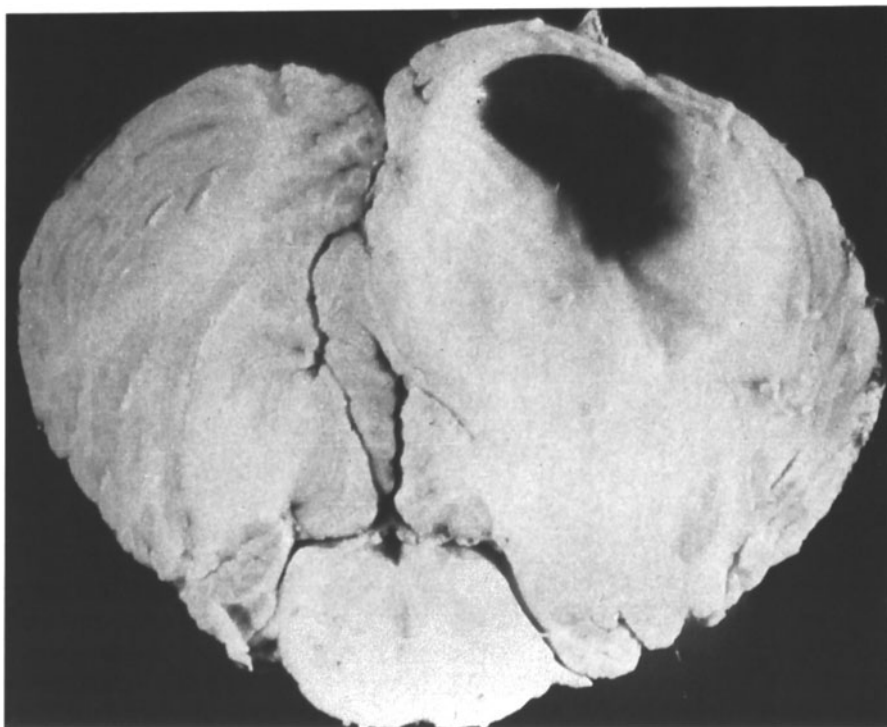


Fig. 9.47. Cerebellar astrocytoma

(Fig. 9.48b). In these areas, cells no longer exhibit a polar, pilocytic aspect; they form many processes and acquire a star shape (Fig. 9.49a). The perivascular processes are usually spared by the degeneration and simulate perivascular condensations which are called “bushes.” There is no unanimous agreement on the primitive or secondary nature of the stellate cell in the vacuolated areas. It is likely that both origins are possible.

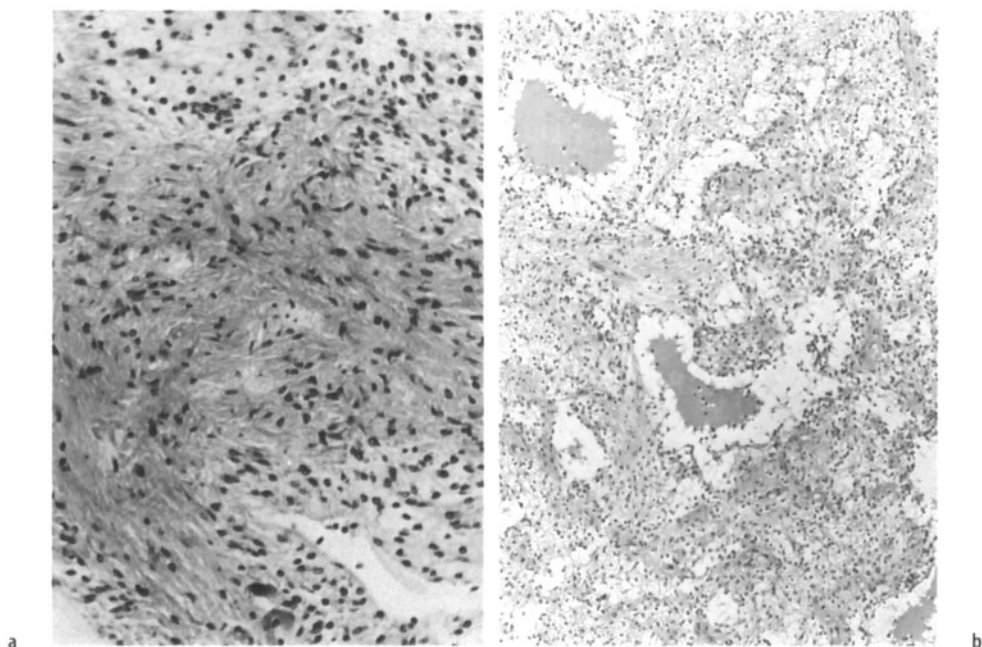
The compact aspect goes under the definition of “pilocytic adult type” and the loose one under that of “pilocytic juvenile type” [2904]. A diffuse type of astrocytoma and even a protoplasmic can also be found.

Often, oligodendroglial features occur, recalling the “honeycomb” aspect of oligodendrogliomas (Fig. 9.50a). In some tumors they appear as secondary degenerative phenomena related to the vacuolar-mucoid degeneration [3799]. According to many authors, on the contrary, foci with true oligodendroglial aspects do occur [373, 2903, 659, 1453], even if cerebellar oligodendrogliomas have only rarely been described [1561, 3730].

Both the bipolar cells in the solid areas and the stellate ones in the loose areas are GFAP positive, thus allowing the processes to be clearly seen even in cross-section. The same structures are demonstrated with vimentin [3022] and are weakly highlighted by detecting glutamine synthetase [3230].

The histological appearance of cerebellar astrocytoma has been variously categorized. In parallel with the pair fibrillary-protoplasmic, the pair pilocytic of adult or



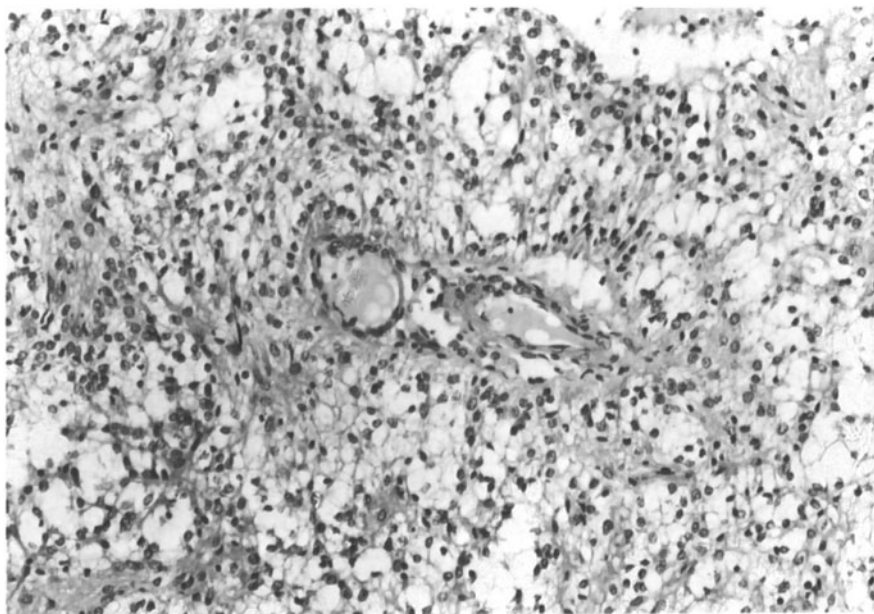


**Fig. 9.48a,b.** Cerebellar astrocytoma. **a** Pilocytic aspect of adult type. H&E,  $\times 300$ . **b** Pilocytic aspect of juvenile type and microcyst formation. H&E,  $\times 150$

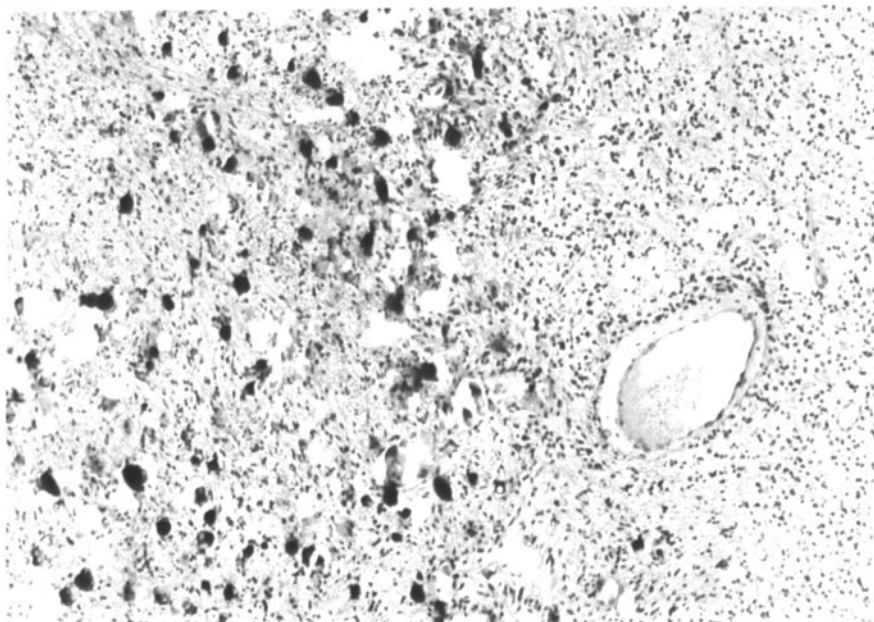
juvenile type has been proposed, depending on the diffuse presence of microcysts or of a more compact arrangement of cells and their processes [2903]. Other pairs have been proposed [1453, 1454], such as that of pilocytic “juvenile type” and diffuse [400], but these distinctions do not contribute fundamentally to a better nosologic position of the neoplasia. Often, different features with various expressions coexist in the same tumor.

Calcifications are relatively frequent (Fig. 9.49b). They have been found in varying percentages: 14% [2994], 22% [3698], and 26% [2899]. Blood vessels of small and medium caliber are quite regularly distributed and often tend to group, forming a sort of network with nodal points. Endothelial hyperplasia with the formation of true glomeruli sometimes arranged in long tracts and showing mitoses is often present (Fig. 9.50b). The endothelial hyperplasia never reaches the intensity typical of glioblastoma. Its frequency has been variously calculated: 52%–53% [3698], or 78.9% [1453, 1454] of cases. Sometimes the formation of blood vessels may be so marked as to suggest the picture of angioglioma, similarly to that which can be observed in other locations. The endothelial hyperplasia does not represent for most authors an unfavorable prognostic sign, as in hemispheric astrocytomas [1936]. This finding is of great importance in the prognostic evaluation made from the histological examination of small fragments.

At the periphery, the tumor has indistinct borders with the healthy tissue. In some areas, it is better delimited and acquires a more compact and clearly pilocytic appearance. In these zones, Rosenthal’s fibers are frequent. The cerebellar folia may be

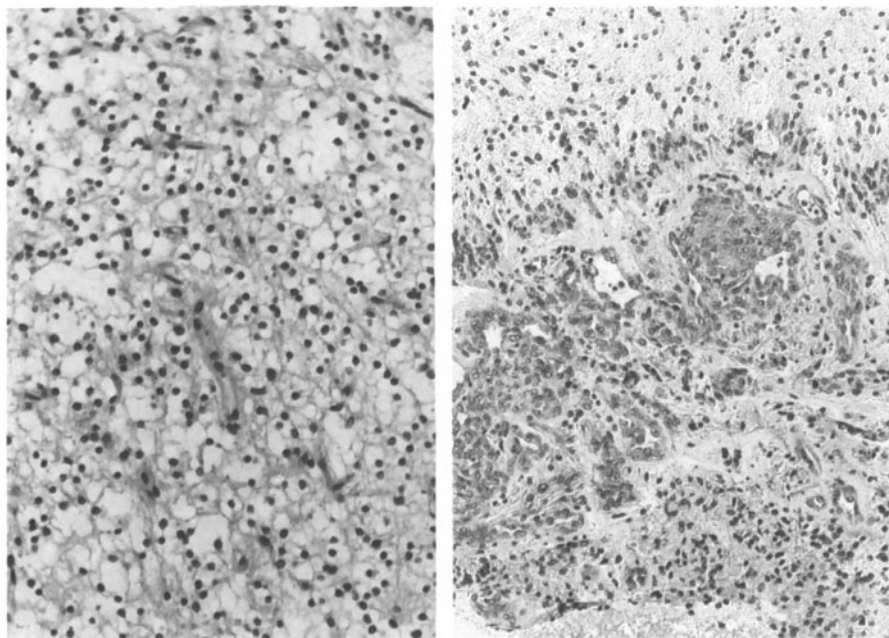


a

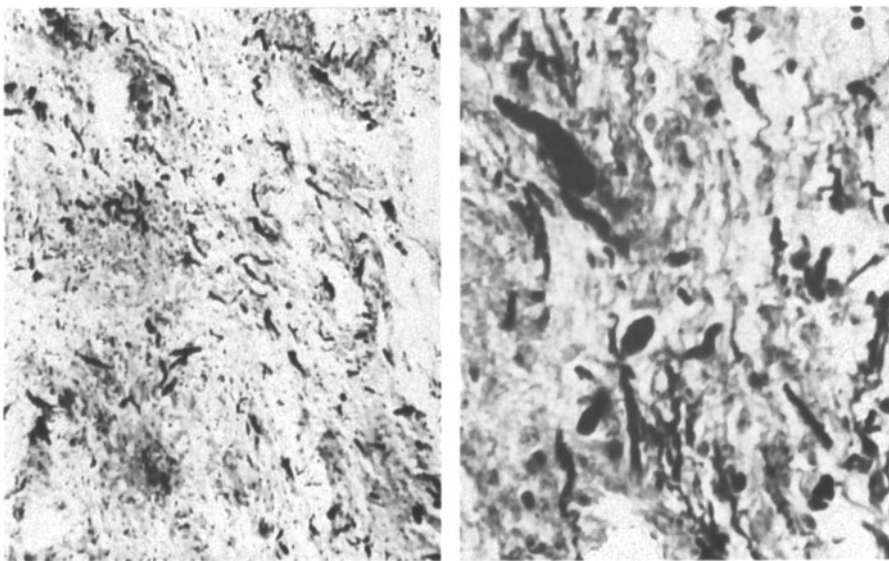


b

**Fig. 9.49a,b.** Cerebellar astrocytoma. **a** Loose architecture. H&E,  $\times 300$ . **b** Calcifications. H&E,  $\times 200$



**Fig. 9.50a,b.** Cerebellar astrocytoma. **a** Oligodendroglia-like aspect. H&E,  $\times 300$ . **b** Vascular glomeruli. H&E,  $\times 200$ . (From [2994])



**Fig. 9.51a,b.** Cerebellar astrocytoma, Rosenthal's fibers. Ferric hematoxylin, **a**  $\times 200$ , **b**  $\times 400$

involved by the tumor and show a scleroatrophic appearance. The tumor may grow exuberantly in the leptomeninges over the cerebellar folia in a desmoplastic pattern.

#### 9.3.5.5

##### *Rosenthal's Fibers*

Rosenthal's fibers are elongated, carrot, comma-shaped, or roundish structures depending on the cutting section. Generally, they have a rounded pole and an extremity terminating in a thin process which gets lost in the glial network (Fig. 9.51). They have a characteristic staining pattern.

They are characteristically found in glial tumors of the midline, especially in the cerebellum, but they have also been described in various pathological conditions involving the subependymal glia: different tumor types, e.g., ependymomas, hemangioblastomas, craniopharyngiomas [3799, 1159], ependymal granulations [2505, 733, 2994], syringomyelia [1643, 603]. They have also been noted in locations not related to the subependymal glia, such as in the white matter of the cerebral hemispheres, in Alexander's disease [1306], in multiple sclerosis [2475], and, in our experience, even in the cerebral cortex around meningiomas. They have also been seen in cultures of astrocytomas of the optic nerve [1194], cerebellum, and spinal cord [1190, 1664].

They are not, therefore, characteristic of midline and cerebellar astrocytomas, but rather reflect the involvement of the subependymal glia independently of the type of process, tumoral, inflammatory, or otherwise. They are structures devoid of enzymatic activity [1194, 2398, 3002, 1234].

Under the electron microscope, they are composed of masses of degenerated glial filaments [1414, 849, 1192]. They form through an interfibrillary accumulation of osmiophilic material, followed by a granular fragmentation of the filaments [3046]. Small osmiophilic masses and filament overload seem to be the basic elements [1193].

The majority of large Rosenthal's fibers are GFAP negative or only show a thin peripheral positive rim [3533, 3230]. This depends on the quantity of amorphous osmiophilic granular material contained. In fact, the small Rosenthal's fibers, with scarce material of this type, are GFAP positive [2124, 3230]. This means that the central amorphous material derives from the aspecific degeneration of glial filaments.

Immunoelectron microscopy with colloidal gold demonstrated that the GFAP antibody is localized mostly on the glial fibrils (Fig. 9.52), but it is also present on the amorphous material [735]. The process begins with the accumulation of glial filaments and carries on with their gradual transformation into amorphous material. It has been shown that the peripheral parts of Rosenthal's fibers and also the GFAP-positive compact bundles of fibrils are ubiquitin-positive (Fig. 9.52) [2026]. This could prove that the accumulation of GFAP is abnormal and destined to proteolysis but that the ubiquitin-dependent proteolytic system is overloaded, hence the formation of inclusion bodies; alternatively, the ubiquitin could be involved in a cytoprotective process tending to isolate the abnormal protein [742].

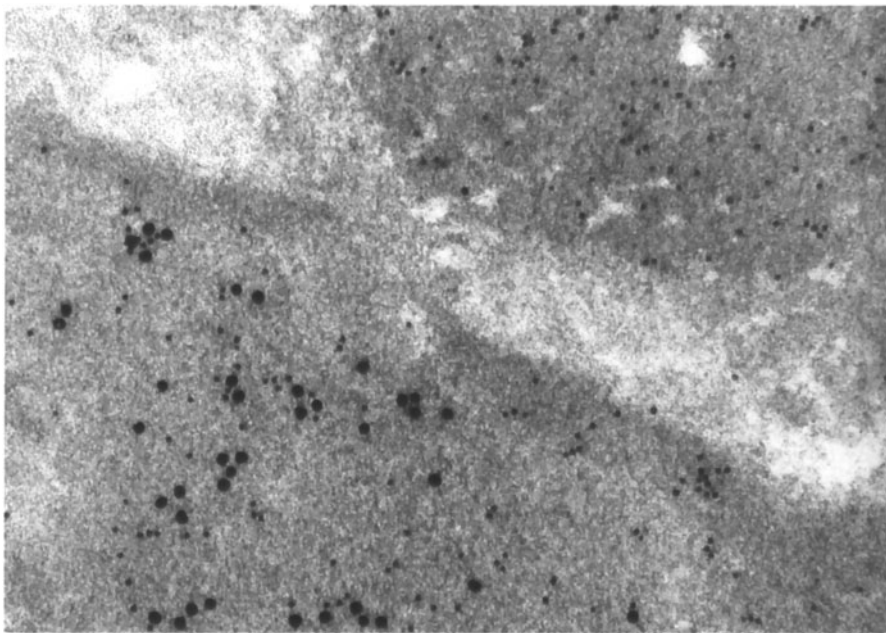


Fig. 9.52. Cerebellar astrocytoma, Rosenthal's fibers. Double immunogold labeling for glial fibrillary acidic protein (GFAP) (*small granules*) and ubiquitin (*large granules*). Both are present in the periphery, and only GFAP is present in the amorphous core,  $\times 80\,000$

#### 9.3.5.6

##### *Malignant Transformation, Prognosis*

The cerebellar astrocytoma is a tumor with a good prognosis, with survival periods up to 25–39 years after total removal or 10–25 years after subtotal removal [1041]. Recurrences are much more frequent after subtotal than total removal [1452]. Some 94% of patients survive 10 years [3698] and 25% for 25 years [1089]. In other series, the percentage of survivors at 5 and 10 years is 94% and 88%, respectively, for children and 83% and 71% for adults [1884]. In still another series of children, 88% survived to 10 years with no sign of recurrence [1023]. The treatment of choice is without doubt surgical removal, but the strategy to follow is controversial in cases of subtotal removal, because permanent cure may follow a partial excision. According to some, radiotherapy is indicated [659], as it is advised for relapses [1872]. However, the radiobiological rationale for radiotherapy is lacking in this tumor. The empirical finding of longer survival after radiation is cast into doubt by the observation that long survival is known even without irradiation [1111, 1041] and that the survival of irradiated and not irradiated cases is in some series practically the same [1023]; a trend toward a lower recurrence rate in irradiated patients with subtotally removed tumor has been reported [1024].

There are a notable number of late recurrences. It has been found that the tumor violates Collins' law, which states that a patient may be considered cured from a tu-

mor if he has survived without signs of recurrence for a period equal to the age at diagnosis plus 9 months. This violation occurs both because there are very late recurrences and because patients who underwent partial removal appear to be cured as well [110]. Recurrences obviously do not necessarily correspond to the malignant transformation of the tumor, which is a very rare event.

Cases have been reported in which the tumor has been found in old age with a very long preoperative duration [1658].

Besides the rare examples of malignant transformation of cerebellar astrocytoma [2795, 596, 211, 3107, 373, 1707, 106, 47] even after some decades [3701, 445], there are equally rare reports of primitive glioblastomas or anaplastic astrocytomas [744, 2034, 2552, 3435, 3792]. The distinction between anaplastic astrocytomas and glioblastomas is not at all easy, and according to some authors, they have to be considered as one unique tumor entity [2034, 3435]. In a review of the literature [1454], only 53 cases of glioblastoma and no more than 50 of anaplastic astrocytomas were found as reported. According to others, up to the end of 1985, not more than 65 glioblastomas have been reported [3301] and 77 to the end of 1989 [2842]. For others, malignant cases are not so unusual (five out of 19 cases [3172]).

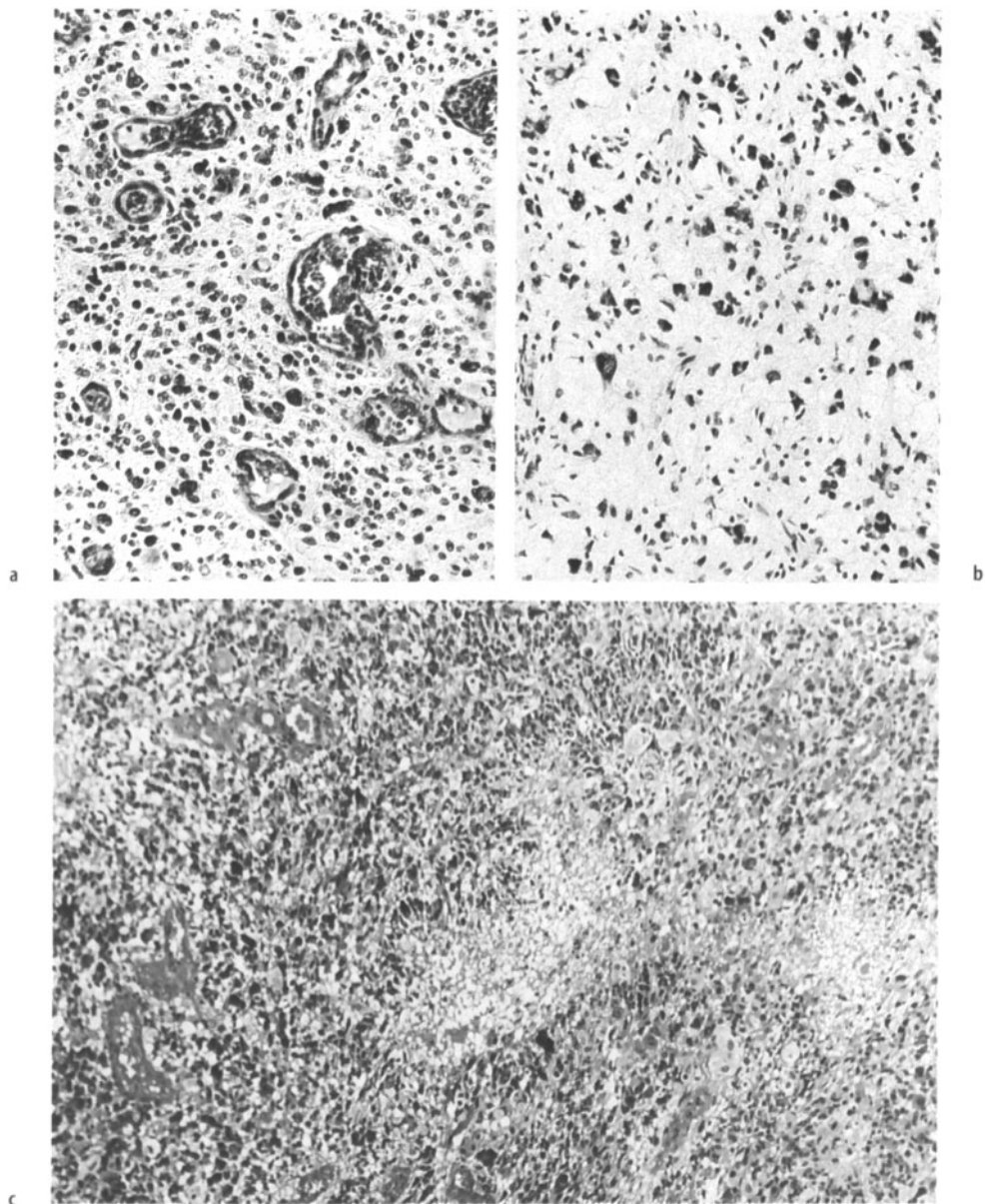
Two thirds of patients are adults [744], with a bimodal age distribution peaking in the first and sixth decades [3792]. The rarity of glioblastomas in the cerebellum has also been explained by the lower tendency of cerebellar astrocytes to undergo anaplasia in comparison with the cerebral ones [848]. Cases with anaplastic features (Fig. 9.53), albeit focal, carrying a poor prognosis undoubtedly exist [1651]. In a personal series, there were six anaplastic astrocytomas from a total of 108 cases, but they did not show a different survival rate to nonanaplastic tumors.

In principle, the tumor grows slowly, and the application of "grading" according to Kernohan et al. [1661] has little value, since few grade 3 and 4 tumors have been recorded [2058, 1111].

The identification of prognostic signs by the statistical analysis of survival has also been tried for this tumor. While a typical histological appearance has a 94% survival rate at 25 years, infiltrative growth was associated with only 38% survival [1089]. The association of microcysts, leptomeningeal growth, Rosenthal's fibers, and oligodendroglial foci in a series of all cerebellar gliomas had a clearly better prognosis than the association of necroses with high cellular density, mitoses, and perivascular pseudorosettes [3698]. Nuclear polymorphism resulted to be an unfavorable prognostic sign only when marked [1454]. Also, the presence of mitoses in any numbers, marked cellular density, marked desmoplasia, and necrosis have the same significance. Hypotheses have been formulated on the possible role of radiotherapy in the development of malignant astrocytomas of the cerebellum. Cases have been reported after radiotherapy for medulloblastoma [2507, 1716], lymphatic leukemia [2708], and craniopharyngioma [2057]. A malignant transformation of irradiated astrocytomas 28 and 13 years later has also been reported [373, 848].

The possibility of identifying malignancy by neuroimaging is very important; the occurrence of edema and mass effects have been exploited in this sense [3792, 2471], but they do not seem to be of great help.

In anaplastic astrocytoma and cerebellar glioblastoma, radiotherapy is indicated [1747].



**Fig. 9.53a–c.** Cerebellar astrocytoma. **a,b** Nuclear polymorphism. (From [2994]). **c** Circumscribed necrosis. H&E,  $\times 200$

## 9.4 Astrocytic Tumors of the Spinal Cord

### 9.4.1

#### Frequency, Age

Astrocytomas occur much less frequently in the spinal cord than in the brain, and this may be related to the difference in weight of the two organs. They are more commonly situated in the thoracic region, followed by the cervical, lumbar, and sacral areas. The most affected decades of life are the third, fourth and fifth. Children may also be affected, but the ratio with intracranial tumors decreases from 20:1 in adults to 10:1 in children [1748].

### 9.4.2

#### Macroscopic and Microscopic Appearance

The macroscopic appearance is usually that of swelling of the cord, often over several segments. The consistency is usually hard and fibrous-like, but it can also be soft if areas of degeneration are present. Cysts may be present.

The cellular density is medium to low, and the cells have a stellate astrocytic appearance, even though their cytoplasm is often not well demarcated. Given the low cellular density, it is sometimes difficult to understand from the appearance of the nuclei alone whether or not one is dealing with a true tumor, unless the nuclei are decidedly polymorphous. Therefore, the diagnostic distinction from reactive gliosis is sometimes difficult. Blood vessels are scarce and of small caliber. Rosenthal's fibers may be present. They are not pathognomonic of the neoplasia in that they may also be found in reactive processes, for example, the walls of a syrinx cavity.

The tumor may undergo anaplastic changes with an increase in cellular density, the appearance of circumscribed necroses, and endothelial proliferation which can suggest the picture of anaplastic astrocytoma or frank glioblastoma.

The prognosis can be established on the basis of histological appearance. Survival seems to be influenced by the type of treatment, i.e., total or subtotal removal or decompression with biopsy [2757]. The usefulness of radiotherapy is highly controversial because of the frequency of well differentiated tumors. However, in contrast to ependymomas, only 6% of intramedullary astrocytomas can be removed completely, even with microsurgery techniques [520]. Postoperative radiotherapy has resulted in improved long-term survival rates. Survival at 5 and 10 years was 58% and 23% [1748], and 60% and 40% [520], respectively, in two series. The recommended dose is 50 Gy [520].

In infancy, radiotherapy is only carried out in the event of recurrence after a second operation, so as to avoid severe damage to the developing nervous system [837].



## Oligodendroglial Tumors

### 10.1

#### Oligodendroglioma

##### 10.1.1

##### Frequency, Age, Site and Clinical Features

Oligodendroglioma has not encountered great nosological difficulties, as it was recognized at the very beginning of modern studies [133, 129]; however, it has seen its boundaries widen or narrow depending on the interpretation of some histological aspects. As a consequence, its frequency varies greatly in the different series, ranging from 1.3% [627] to 9.6% [3803] of all intracranial tumors and from 5% [2901] to 18% [3803] of all gliomas. In the present series, they represent 4.2% and 9%, respectively. It is typically a tumor of adults, but the average age is difficult to ascertain, because there is a notable discrepancy between the time of onset of the first symptoms, diagnosis, and surgical intervention. From Cushing's various series, an average age of 28 years has been derived. Other series have reported averages of 36 [798], 37 [2740], and 44 years [2994]. In Zülch's series [3803], the age peak was between 35 and 40 years. It is rather rare in infancy. However, cases have been reported [1034, 2271, 3797, 207, 3111, 2596, 3524, 2528] even in neonates or in breast-fed infants [3350, 1737].

The tumor develops in the white matter of the hemispheres with a predilection in decreasing order for the frontal, parietal, temporal, and occipital lobes [3799, 2541, 2097, 3091, 2994, 494]. Spinal cord [959] and cerebellar [2528] locations are rare.

Clinically, a long preoperative history with epileptic seizures is quite common. In terms of the diagnosis, epilepsy is very important, especially if it begins in middle-aged patients. Focal neurological symptoms and headache follow. A syndrome of increased intracranial pressure may occur, especially if the tumor enters the ventricles.

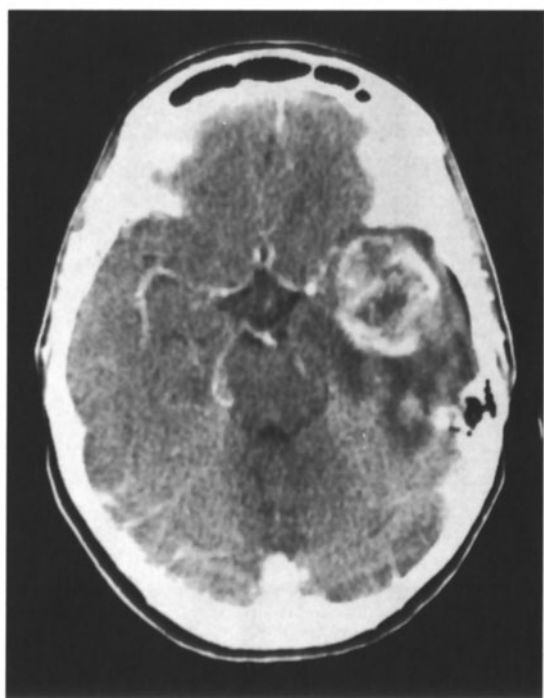
##### 10.1.2

##### Macroscopic Appearance and Imaging

The tumor has a fairly characteristic appearance. By infiltrating the cortical gyri from the white matter, it takes on a "garland" appearance and frequently burrows itself mushroomlike passages. It may invade the meninges and reach the dura, or it may grow deep and penetrate into the ventricles, or even be predominantly intraventricular [2119] (Fig. 10.1).



a



b

**Fig. 10.1. a,b** Frontotemporal oligodendroglioma. **b** Temporal oligodendroglioma enhanced on computed tomography (CT) scan and with calcifications

It has a variable soft or gelatinous consistency and is gray-pink in color, sometimes cystic, and often calcified. The tumor limits are often sharp on the surface and ill-defined deeper down.

On computed tomography (CT) scan the most frequent sign is represented by calcifications. The tumor appears as a hypodense, well-circumscribed lesion, and on magnetic resonance imaging (MRI) as a lesion of low intensity. Contrast enhancement for CT and gadolinium may indicate higher-grade lesions. Necroses and hemorrhages may be present.

### 10.1.3

#### Microscopic Appearance

The tumor has a medium to high cellular density. The cells are fairly round and regular and have scanty cytoplasm, sometimes with short processes (Fig. 10.2a). The nucleus has a fairly characteristic chromatin pattern with a central nucleolus. These characteristics are typical of normal oligodendroglia, even in its variations, and are clearly evident in acetic carmine preparations (Fig. 10.3a,b) [2987]. The nuclei may also be large or polymorphous, but this does not constitute an indicator of malignancy per se. Mitoses are found in moderate numbers. The cells are arranged without a particular pattern or are organized into more or less large lobules delimited by the septa of blood vessels. The cells may take on particular configurations when they cluster around blood vessels or around neurons in infiltrated cortical areas. Elegant images of perineuronal “satellitosis” may form (Fig. 10.2b), very useful in the differential diagnosis, even though not pathognomonic of the tumor.

One of the characteristics of this tumor is the appearance of a perinuclear “halo” which imparts to the area a “honeycomb” appearance (Fig. 10.4a). This is an artifact, due to fixation and to the presence of “mucoid” material (i.e., glycosaminoglycans, GAGs) in the cytoplasm. In the earlier literature it was described as the degeneration corresponding to the “acute swelling” of the oligodendroglia of Penfield [2600] or the mucoid degeneration of Grynfeldt [1181]. Histochemical reactions for GAG are strongly positive in these areas (Fig. 10.4b) [3000, 2994, 1077], and the “honeycomb” degeneration is the most typical of the areas associated with an accumulation of GAG [1077], in analogy to what occurs in experimental ethylnitrosourea (ENU)-induced oligodendrogliomas [2176], even if the pathogenetic connection is not known. Various types of GAG may be identified, in particular, chondroitin sulfate [221]. The honeycomb appearance is a nonpathognomonic, regressive process, but nonetheless it is of notable help in the differential diagnosis. Microcyst formation may be related to these events.

The blood vessels have a typical distribution: They form short and angulated segments, like the branches of a tree, and tend to delimit lobules. They often have thickened, sometimes hyalinized walls and occasionally show endothelial hyperplasia (Fig. 10.5a).

In circumscribed areas, there may be cells of uncertain origin with scanty but clearly visible eosinophilic cytoplasm and with a half moon peripheral nucleus, which are called minigemistocytes. Calcifications are characteristic of oligodendroglioma. Different types may be distinguished [2131, 3799, 2988] (a) pseudocal-

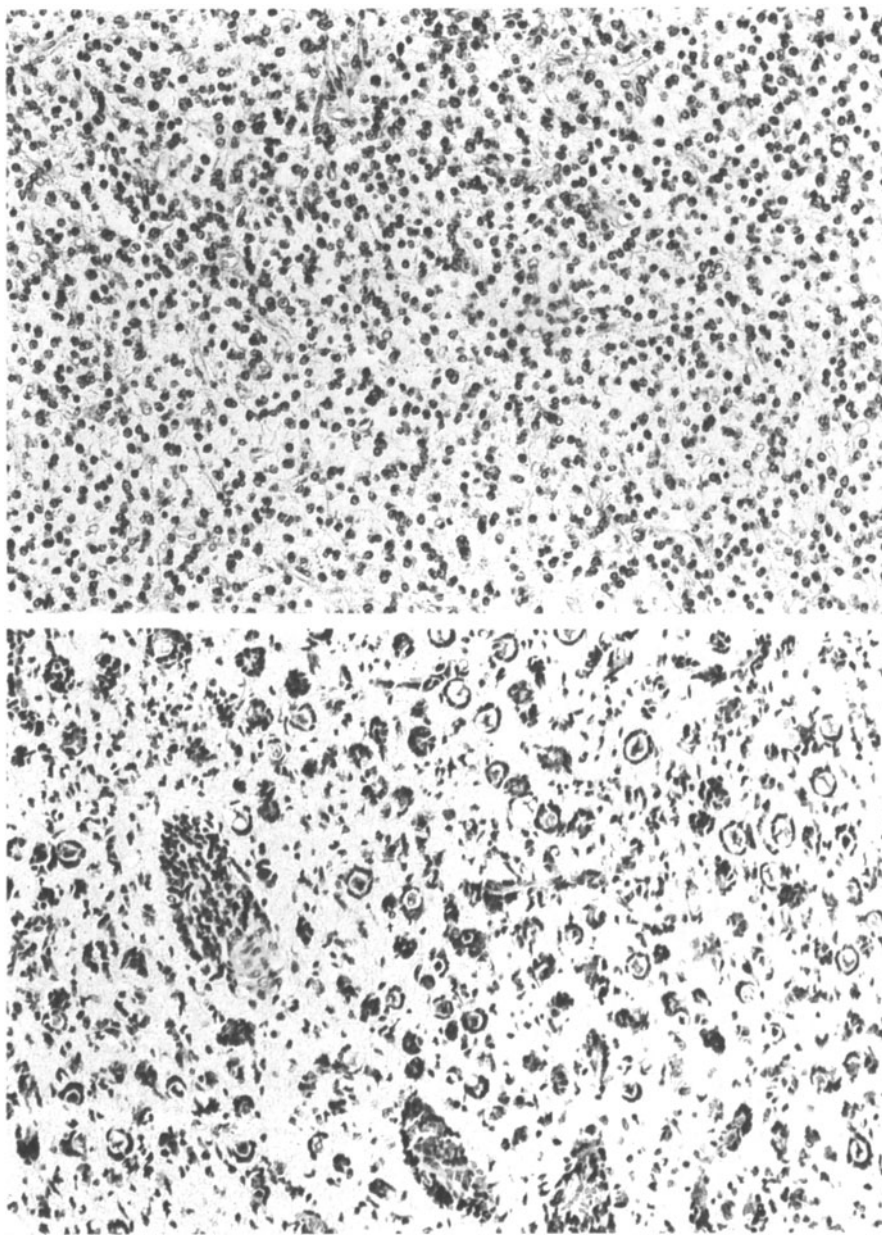
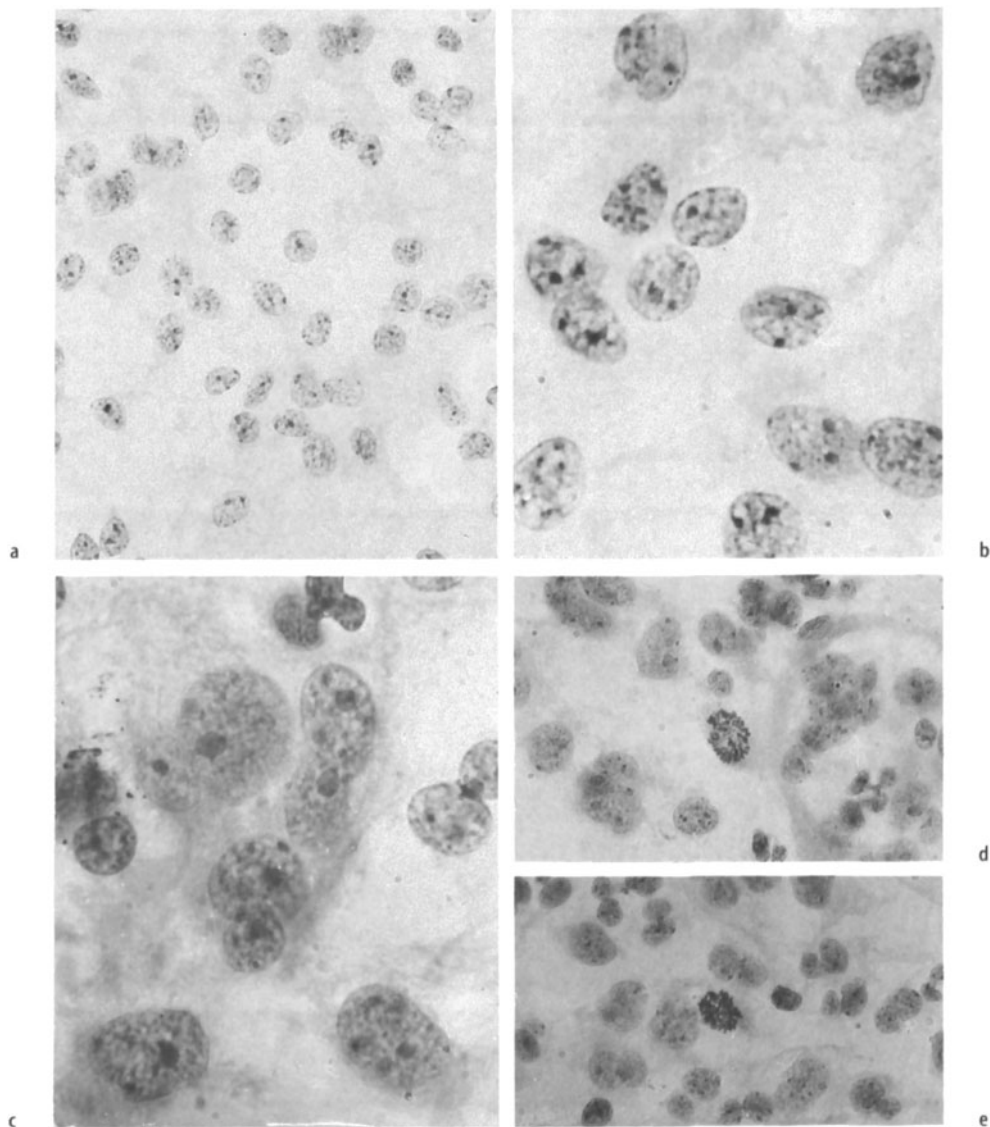
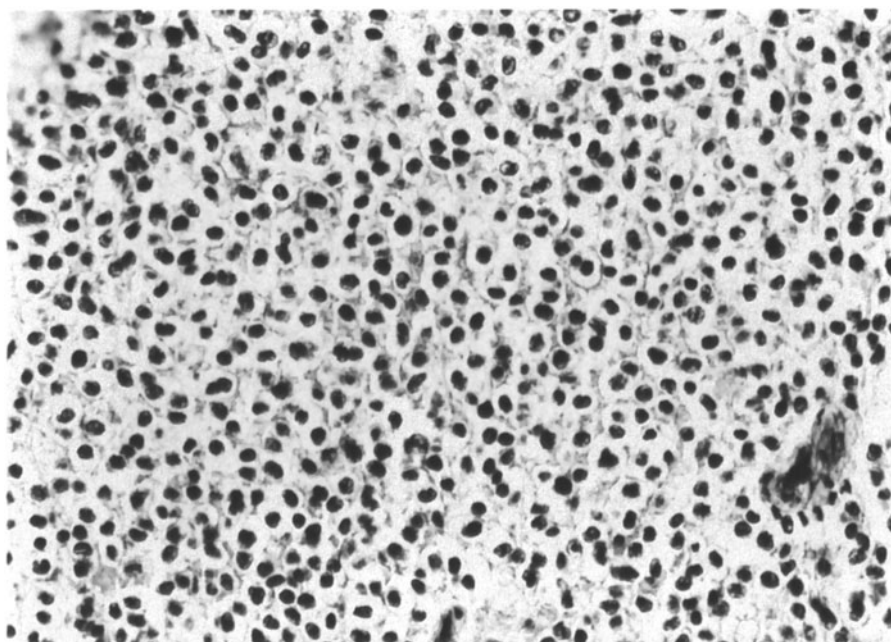


Fig. 10.2a,b. Oligodendroglioma. a Isomorphic aspect of tumor cells. b Cortical perineuronal satellitosis and perivascular growth. H&E,  $\times 200$

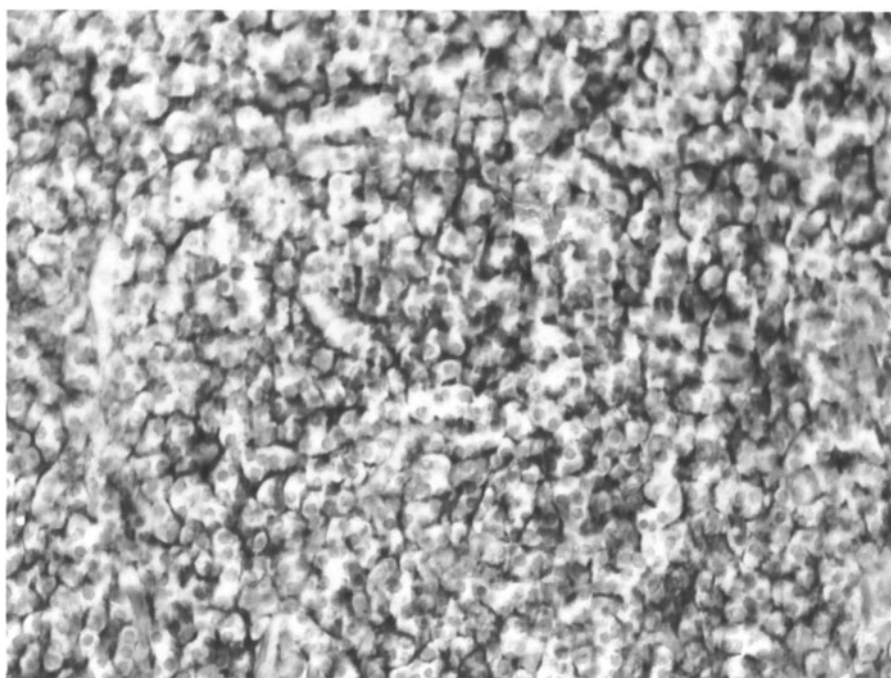


**Fig. 10.3a–e.** Oligodendroglioma. **a,b** Typical distribution of chromatin in the nuclei. **c** Anaplastic variant. **d,e** Mitoses. Acetic carmin, **a–c**  $\times 400$ , **d,e**  $\times 1000$ . (From [2987])

cium-calcium (pCa-Ca) precipitations on capillaries or in the media and adventitia of larger vessels in the form of fine granules; these may become confluent and surround a blood vessel, like a sleeve, or be arranged in larger, roundish, lobulated deposits; (b) apparently homogeneous precipitations involving entire segments of blood vessels, the media, adventitia, or both in larger blood vessels; (c) roundish calcifications with polylobulated, rounded borders with annular stratifi-

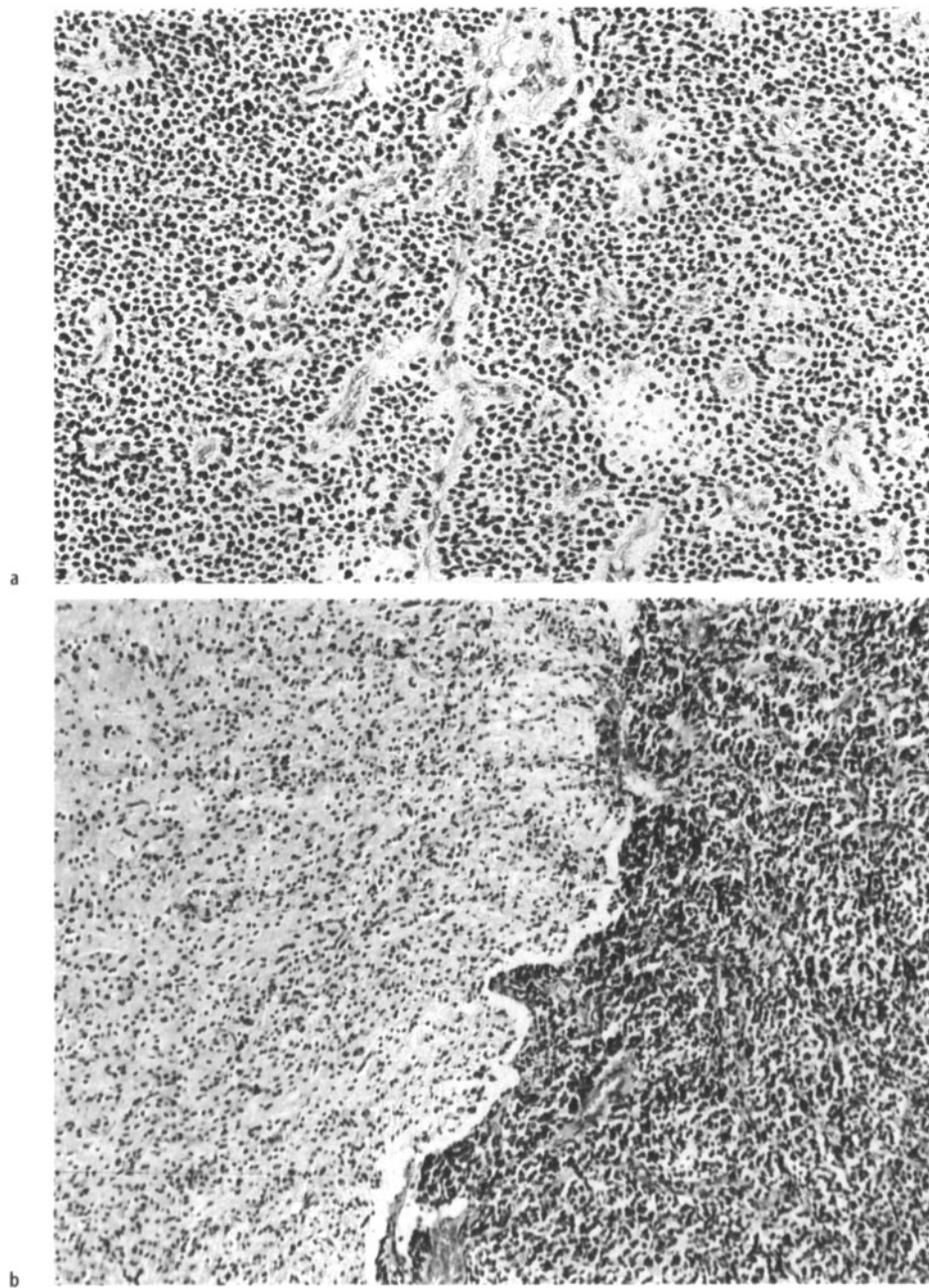


a



b

Fig. 10.4a,b. Oligodendroglioma. a Perinuclear halo, H&E,  $\times 300$ . b Alcian blue-positive staining of the honeycomb aspect,  $\times 400$



**Fig. 10.5a,b.** Oligodendroglioma. **a** Typical distribution of vessels. **b** Subarachnoid growth. H&E,  $\times 200$ . (From [2994])

cation and variable dimensions; and (d) roundish formations apparently not related to blood vessels.

The calcifications may lie deep in the tumor, but they are particularly concentrated at its periphery or in the adjacent infiltrated normal tissue. They often accumulate in foci, in which histochemical examination identifies an older center and a more recent periphery. Generally, the blood vessels are the most important substrate for calcification, but neuroectodermal structures such as neurons, which have become entrapped in the tumor, may also act as a substrate for the precipitation. The frequency of calcifications in oligodendroglioma is very high, occurring in 70% of the present series. Sometimes they are visible radiologically, with a convoluted appearance as in Sturge–Weber disease.

The tumor grows by infiltration and, in general, it ascends from the white matter into the cortex. It is, however, common to find infiltration of the cortex, especially along penetrating blood vessels from the meninges, originating from a subpial proliferation. In this event, the infiltration of the cortex decreases, going towards the white matter, or it merges with that coming from the white matter. The tumor grows in the meninges and may be adherent to the dura (Fig. 10.5b).

Many blood vessels demonstrate adventitial infiltration by lymphocytes and plasma cells, especially at the periphery.

Oligodendroglioma may sometimes spread via the cerebrospinal fluid (CSF) and rarely metastasizes extracranially [1529].

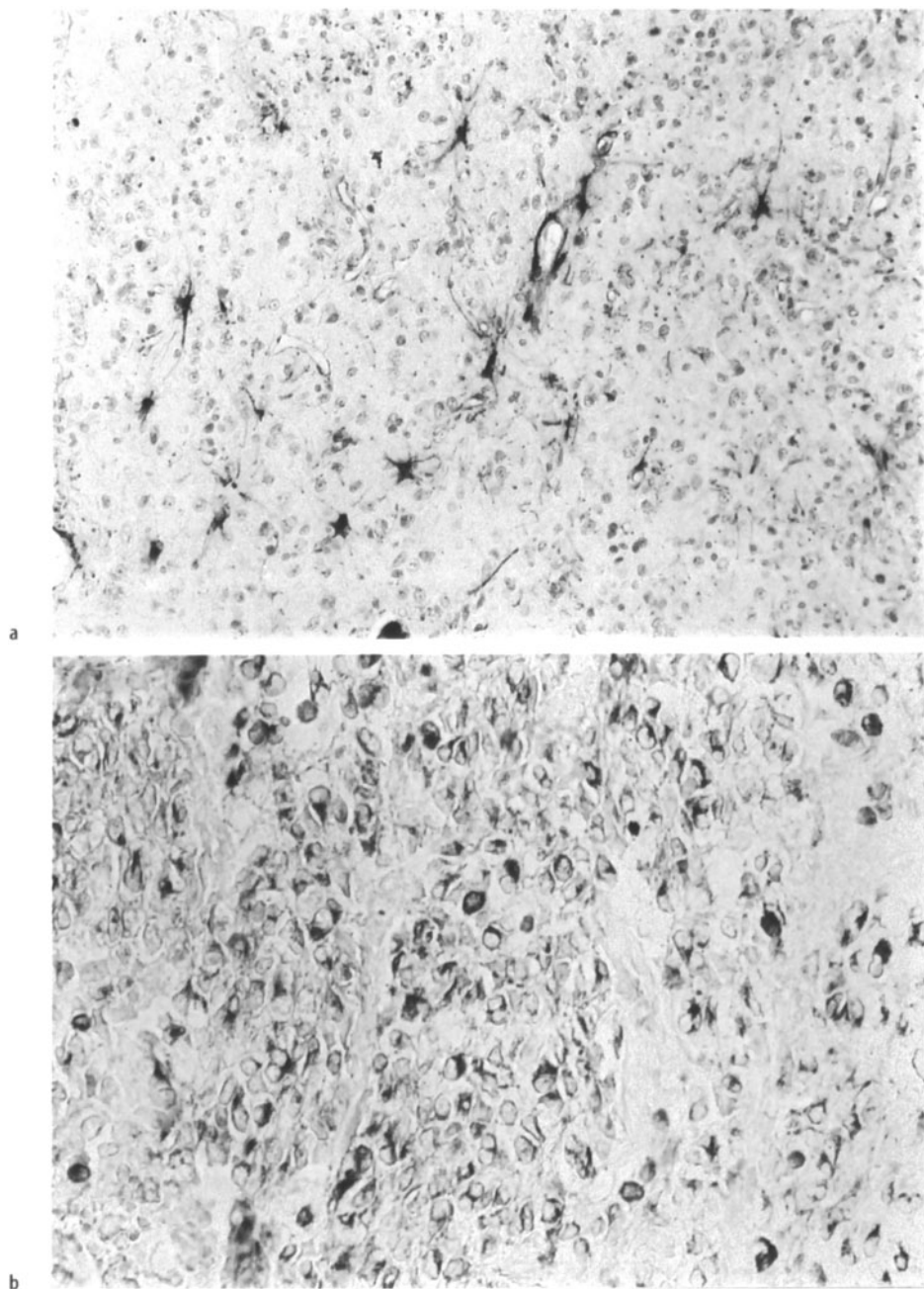
## 10.2

### **Presence of Astrocytes and the Problem of Mixed Gliomas: Oligoastrocytoma**

In the WHO classification, the dignity of oncotype has been conferred to the oligoastrocytoma as mixed oligoastrocytic glioma. This tumor is characterized by the presence of numerous astrocytes, apart from oligodendrocytes. The pathogenesis of this mixed tumor, however, is unclear. The demonstration of glial fibrillary acidic protein (GFAP) has brought an important contribution showing that, apart from the clearly recognizable reactive astrocytes included in the tumor, there may be GFAP-positive neoplastic astrocytes (Fig. 10.6a) [2385], belonging to the astrocytic component of the mixed tumor, and GFAP-positive cells of dubious oligodendroglial appearance (Fig. 10.6b) [3507, 668, 2238, 3018]. These cells have been interpreted either as small gemistocytic astrocytes, without demonstrable gliofibrils [668], or as transitional cells between oligodendrocytes and astrocytes [3507], corresponding to bipotential precursors [2703], or as an expression of transition forms between classic oligodendrocytes and oligodendrocytes expressing GFAP [1307]. The last is reminiscent of the myelin-forming glia which, during development, transiently expresses GFAP [503]. The tumor is, therefore, a further subtype of mixed oligo-astrocytic oligodendroglioma. There are also alternative interpretations: One is that GFAP-positive astrocytes form halos with the assumption of oligodendroglial characteristics [1579].

A comparison between tumor oligodendrocytes expressing GFAP or “gliofibrillary oligodendrocytes” (GFOC) and minigemistocytes showed that, on electron microscopy, GFOC possess glial filaments oriented in parallel bundles. There is, therefore,





**Fig. 10.6a,b.** Oligodendroglioma. **a** Glial fibrillary acidic protein (GFAP)-positive stellate astrocytes. PAP-DAB,  $\times 200$ . **b** GFAP-positive, round minigemistocytes. PAP-DAB,  $\times 400$

a transition between the two cell types reflecting the conversion of neoplastic oligodendroglial to astrocytic lineage [1784].

Besides GFAP-positive minigemistocytes and gliofibrillary oligogemistocytes, there are also classic large GFAP-positive gemistocytes [1783].

Today there are numerous markers for oligodendrocytes, for example, the monoclonal antibody against Leu-7, anti-myelin associated glycoprotein (MAG), antibody against myelin basic protein (MBP), and antibody to carbonic anhydrase C. However, it is very difficult to use them for diagnostic purposes in paraffin sections, especially from embedded tissues. According to some authors, marking with the Leu-7-specific antibody is positive in a high percentage of cases, especially in the cytoplasmic membranes and processes [2385]. It is reliable in the diagnosis of oligodendroglioma [2338]. However, not all cases are positive, even though in tumors in which anti-Leu-7 reacts with the neoplastic cells, more than half the tumor cells are positive [2613]. It must be taken into account that this antibody also reacts with other CNS and PNS tumors [1975, 2613], although in a smaller proportion of cells.

The MBP-specific antibody does not react with tumor cells, but with myelin sheaths, whilst the MAG-specific antibody reacts only with occasional tumor cells. Carbonic anhydrase C antibody reacts only with a few tumor cells, while it is widely positive in normal oligodendrocytes both in man [2385] and rat [1080]. Oligodendrogliomas react immunohistochemically with antibody to A2B5 and GC, thereby demonstrating a derivation of the cells from the A2B5-positive progenitor, in common with astrocytes. In mixed oligo astrocytic tumors, by contrast, there are cells which are positive for both GFAP and A2B5 [673].

### 10.3

#### Anaplastic Oligodendroglioma and Prognosis

Oligodendroglioma may become malignant in time, even though this transformation is not so frequent as for astrocytoma.

Anaplastic oligodendroglioma is characterized by an increase in cell density, nuclear polymorphism (Fig. 10.7a), and the number of mitoses. Endothelial proliferation (Fig. 10.7b) becomes more apparent, and circumscribed necroses appear (Fig. 10.8). The picture may be so remarkable as to resemble that of glioblastoma. The recognition of the oligodendroglial origin is based on the persistence of differentiated tumor areas.

In the malignant transformation of oligodendroglioma, cells with astrocytic features may appear, represented mainly by the small GFAP-positive, microgermistocytic, round cells already described [400]. These cells contain intermediate filaments [2951].

Because endothelial hyperplasia and mitoses are commonly found in oligodendroglioma, the identification of the anaplastic variant in its initial stages is not easy. A difficult and long debated problem is, in fact, that of the predictability of survival on the basis of the histological appearance. The application of a "grading" which proved to be both useful [798] and not useful [2353] has not overcome the problem. The tumor shows an apparent morphological homogeneity but in reality is characterized by multiple features, including the presence of mitoses, even in cases of certain and verified benignity.

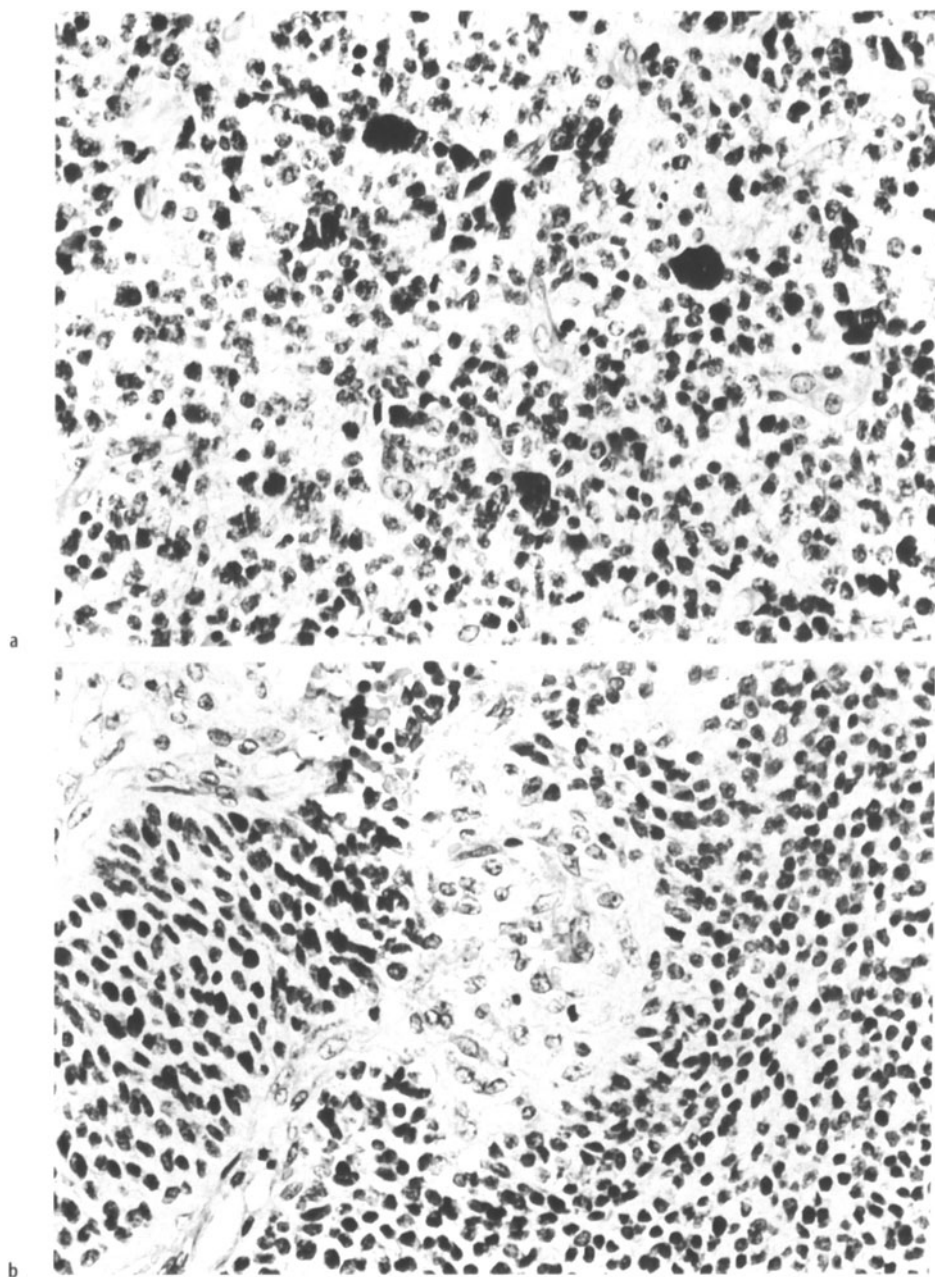


Fig. 10.7a,b. Anaplastic oligodendroglioma. a Nuclear polymorphism. b Endothelial proliferation. H&E,  $\times 200$



Fig. 10.8. Anaplastic oligodendroglioma, circumscribed necrosis. H&E,  $\times 200$

The prognostic importance to be attributed to different histological factors has been the object of numerous studies with contrasting results. In some [3232], only the nuclear pleomorphism has been considered relevant, whilst in others microcyts, necroses and cellular density are important. Patients with tumors with low cell density, microcystic degeneration, and no necrosis survive on average 6 years longer than those who do not show these features [2328]. Less clear-cut is the negative prognostic significance of subpial growth. Also, in other experiences, necroses are a factor of certain prognostic significance, determinantly contributing to the definition of the anaplastic variant of oligodendroglioma.

Opinions diverge on the importance of the number of mitoses, according to whether these are considered [397] as a prognostic factor or not [2328]. This is very important, because, with respect to astrocytoma, they seem to play a much less predictive role. The presence of astrocytic areas does not seem to have any prognostic influence [3232, 397, 3680]; however, gemistocytes are an ominous sign [1783]. It is, therefore, improbable that, as proposed in the past [153, 2353], the malignant transformation of oligodendroglioma is a consequence of the possible transformation of its astrocytic component. In contrast to astrocytomas, there are no significant associations between age and histological factors (for example, the greater incidence of endothelial proliferation with increasing age [397]).

Recently, the importance of the application of "grading" for the establishment of the prognosis of oligodendrogliomas has been reevaluated [3232, 2036, 1782], utilizing systems with four categories which are very similar, even if simplified, to the original ones of Kernohan et al. [1661]. The only significant differences are found between the extreme grades, i.e., between cases characterized by low cell density, little

or no polymorphism, few mitoses, minimal endothelial proliferation, and absence of necroses, and cases defined as anaplastic, with high cell density, marked polymorphism, many mitoses, marked endothelial proliferation, and necroses. There is no significant difference among the intermediate grades [3154].

There is a significant difference in survival grouping together grades 1–2 and 3–4 according to the St. Anne-Mayo system [655] and even greater with the Kernohan system [1661]. A review of the problem has recently been published [2998]. Using a system of three grades [3232, 1786], a positive correlation with survival can be found.

The main problem is recognizing the anaplastic variant in small surgical biopsies. Research on independent prognostic factors to be used in individual cases is thus justified. Proliferation marker immunohistochemistry can be applied. Since there is broad overlapping of labeling index (LI) ranges between the classical and the anaplastic variant, the LI may be prognostic only when greater than the maximum value of the classical variant [2992]. After multivariate analysis, MIB-1 LI can be considered as a prognostic factor [794]. The same significance is attributed to MI [1785]. In other studies, too, MIB-1 LI showed a good correlation with both tumor grade and outcome [1592] and must therefore be considered a good prognostic factor [562]. Ploidy patterns obtained by DNA-flow cytometry did not show any correlation with pathology and behavior [1785], but S phase was found to correlate with tumor grade [562].

The median survival of patients with oligodendrogliomas varies between 3 and 5 years in the larger, recent series [2328, 2036, 383]. Survival is, however, definitely shorter for cases variously defined as “malignant” or as having a “higher degree of malignancy” [3091, 3232, 3340], i.e., 17–21 months. There are, on the other hand, numerous cases with a very long survival of 25–40 years [1390, 2807]. Generally, oligodendroglioma recurs locally, but it may metastasize via the CSF with a frequency varying from 1.2% to 8.5% in clinical studies and around 14% in autopsy-based reports [2036]. Large intratumor hemorrhages may also occur, whilst extraneural metastases are exceptional.

The role of age in clinical outcome is still controversial. In a large series it did not seem to influence survival, whereas in others it appeared to be a prognostic factor [3680, 3232, 397, 3154, 1786]. In some studies, age appeared to be a confounding factor, since younger age correlated with lower histological grade and with more favorable tumor sites, e.g., the frontal lobe [1786]. Frontal sites have a considerably better prognosis.

Amongst the clinical factors which seem to influence the survival of patients with oligodendroglioma positively, are epileptic fits as the first and only symptom, good preoperative clinical status, blood groups O and B, radiological appearance of calcifications, and well-demarcated, nonnecrotic, or hemorrhagic macroscopic appearance, but not age (in contrast to astrocytic gliomas) [2328].

Surgical removal, especially if macroscopically complete, seems to guarantee better survival [1390, 3524, 2328].

The role of surgical resection is still controversial, but most recent studies demonstrate that oligodendroglioma patients survive longer after surgery [580A].

The usefulness of postoperative radiotherapy for subtotally resected cases has always been controversial [1907] and remains so even in the more recent series. According to some [383], it is not useful, while according to others it would improve,

even if modestly, the median survival [1968] or increase the number of long-term survivors [3598]. The controversy is due to the difficulty in assessing the sensitivity of the tumor to radiotherapy, which in turn is due to the rarity of the tumor, to the difficulty in establishing the malignancy grade and to the lack of randomization. Many authors agree on treating patients with definitely malignant and subtotally resected tumors. In children, the usefulness of radiotherapy has not been demonstrated. The alternative of stereotactic radiosurgery is still debated.

For recurrent oligodendrogliomas, the efficacy of systemic PCV (procarbazine, CCNU, and vincristine) has been reported [413, 415]. Responses have also been reported in newly diagnosed aggressive oligodendrogliomas treated with the same chemotherapy combination [2059]. PCV chemotherapy has been proposed prior to radiotherapy. Trials are now in progress on chemotherapy compared with radiotherapy of oligodendrogliomas [932]. Other chemotherapeutic drugs are also now under trial.

## Ependymal Tumors

### 11.1

#### Ependymoma

Ependymoma is a tumor arising in close relationship to the ependymal covering of the ventricular system, as demonstrated by its location and by the morphology of its cells. However, despite its close relationship with the ependymal covering, this tumor may grow deeply into the white matter.

#### 11.1.1

##### Classification Problems

This group of tumors was first outlined by Bailey [126] and by Bailey and Cushing [134] who distinguished ependymomas, composed of ependymocytes, from ependymoblastomas, composed of ependymoblasts. The latter name was subsequently used by various authors to designate the malignant variant of ependymoma. The plexus-papilloma was at first separated from the group [1393, 128], and then reintroduced [1659]. Various types were distinguished: a cellular one with a perivascular cellular arrangement, an epithelial one, characterized by ependymal canals, a papillary one, and the plexus-papilloma [1659].

Another variety, the ependymal spongioblastoma, characterized by the presence of spongioblasts typical of subependymal layers and mitoses, corresponding to the ependymoblastoma [1101] was subsequently recognized. Lastly, the subependymoma was added to these varieties [2973, 2974].

Subsequent authors have, in general, accepted the subdivision into cellular, epithelial, myxopapillary, and subependymoma [2796, 3799, 2903, 1505, 2994, 1147]. The significance to be given to each tumor type and their relationship with the formal origin of the tumor have not been definitively explained. The facts that the epithelial variety is more frequent in infratentorial and spinal locations, that mitoses are the rule in supratentorial tumors and rare in infratentorial ones, and that the myxopapillary variety is exclusively found in the cauda equina cannot alone facilitate the understanding of the formal genesis of the tumor. Instead, it is important to give significance to the individual structures which characterize the tumor. In the description of ependymoma, terms such as rosettes, pseudorosettes, radial crowns, and so forth, which require qualification and also definition from the cytogenetic viewpoint, often recur.

First of all, it has to be remembered that normal ependymal cells arranged around a lumen and hence forming “rosettes” may be found close to the ventricles, in the

folds of the ventricular wall, or around the aqueduct. This finding is very important for the recognition of the significance of these structures inside the tumor, i.e., whether they represent a sign of differentiation or of undifferentiation, as a vestige of the capacity to cover the lumen of the neural tube.

Rosettes, characteristic of ependymomas and neuroepitheliomas, have been defined as structures formed by ependymal cells arranged around a true lumen, akin to the ependymal canal. They imitate the covering of the neural tube [1297]. Instead, structures characterized by a radial arrangement of ependymal cells so that the processes converge towards a virtual central point are called rosettes by some [2861, 575] and pseudorosettes by others [3799]. If a blood vessel is found in the center of these structures, they are considered to be perivascular pseudorosettes, gliovascular formations, or radial crowns. Formations similar to those described can be found in many other oncotypes, so that the problem is extended to involve various differential diagnoses. First of all, rosettes are found in retinoblastoma, where cells are arranged around a central lumen, delimited by a well defined membrane which stains with phosphotungstic hematoxylin. This type of rosette is exclusive to retinoblastoma [1191] and represents the tendency to imitate the neural tube [2749] and to replicate the layer of cones and rods [1033]. Due to the fact that retinoblastoma derives from primitive rather than differentiated retinal cells, the rosettes appear only in the more mature tumors and point, therefore, towards differentiation rather than immaturity.

From the ultrastructural point of view, rosettes are formed by cells featuring "terminal bars," cilia, and microvilli. However, rosettes in retinoblastoma have only one cilium per cell. The cilium features a concentric structure of nine pairs of peripheral tubules and none in the center. The model is called 9+0 [42, 2667] and is typical of cilia of neural derivation [640, 3467]. In ependymoma, on the other hand, the model is 9+2 [2049, 2961]. It has to be remembered that cilia have also been described in astrocytoma [3386] and in extraneural structures, for example, the meninges.

Rosettes are described in medulloblastoma, in which cells send processes towards a virtual central point, similar to the Homer-Wright rosettes of central and peripheral neuroblastomas, pinealoblastoma, and pinealocytoma. Strictly speaking, on the basis of what has been said above, these structures must be called pseudorosettes, which according to some are not at all specific for medulloblastoma and neuroblastoma in that they can be found in various tumors outside the CNS [1191].

When the pseudorosettes are formed around blood vessels, they are called "radial crowns." These have to be distinguished from astroblastic arrangements, characterized by perivascular endfeet and by processes extending into the perinuclear cytoplasm [2904].

On the basis of observations of the comparative anatomy of the common precursors of the ependyma and the adult glia, i.e., the tanycytes (also known as ependymoglia), a "tanycytic" variety of ependymoma has been recognized.

In the neural tube, tanycytes form processes directed towards the ependymal layer and also send long processes towards blood vessels and the pia mater. Similarly, in tanycytic ependymomas, there are bipolar cells with prolongations directed towards blood vessels [966]. These may resemble those of oligodendroglioma in cross section. This variety, which has to be differentiated from pilocytic astrocytoma, is particularly found in the spinal cord. The problem concerning the recognition of ependy-



moma cells as ependymocytes, astrocytes, or transitional cells involves the transition between ependymoma, subependymoma, and astrocytoma. One of the most important points of the whole question involves the transitional characteristics of cells of the subependymal layer which recall the transition from tanycytes to astrocytes [3306] (see Chap. 1).

As already mention in Chap. 1, in humans two types of tanycytes are distinguished on the basis of glial fibrillary acidic protein (GFAP) expression and localization. The first type is found in the walls of the third ventricle and is GFAP positive during development and negative in the adult form. The second type is more diffuse, has no secretory function, and is found in the ventricles, where it covers the white matter. It does not intervene in cellular migration or in the maturation of the ependyma but migrates in the subependymal layer where it remains as a "subependymal" or "transitional" glia. Tanycytes do not represent an immature form of ependymal cell, nor one of its stages of development; they develop in parallel to ependymal cells. This entails that finding tanycytes in tumors does not imply greater or lesser differentiation. A participation of tanycytes in the development of ependymoma had already been suspected [692]. Recently, however, they have been likened to the elements of pseudorosettes of other oncotypes such as astroblastoma, on the basis of their characteristics, which are intermediate between tanycytes and astrocytes, especially from the ultrastructural point of view [2880].

The last version of the WHO classification [1702] recognizes the ependymoma, an anaplastic variant, a myxopapillary variant, and the subependymoma.

### 11.1.2

#### Frequency, Age, Sex, Site and Clinical Features

It is a relatively rare tumor and represents 3%–9% of all neuroepithelial tumors [626, 814, 2796, 3349, 1297, 158, 2994]. It is the most frequent neuroepithelial tumor in the spinal cord, representing 50% [1297] or 60% [1660] of such neoplasias.

Ependymoma occurs in all age groups: 7 months to 81 years [3803], 1 month to 64 years [922], and 4 months to 64 years [1780]. In general, the average age of patients when supratentorial tumors appear is greater than for infratentorial ones [814, 3349, 1780, 922], whereas for spinal tumors it is usually higher than for other locations, varying between 30 and 40 years [814, 2796, 3710].

In infancy, this tumor occurs with a high frequency. Ependymomas represent one tenth of intracranial tumors at this age, and it can be said that half of all ependymomas occur in infancy [745]. In one series, they represented 12% of intracranial tumors [1987].

The average age of children with tumors has been calculated to be 5.4 years, with a range of 2 months to 16.5 years [3749]. In a personal series [3032], children accounted for 36% of all ependymomas. Ependymomas have been described in breast feeding infants [1703, 2054, 1780, 922, 158], and youngest cases are those described by Fokes and Earle (1969) [922] and Abbott and Namiki (1968) [2] in 4- and 6-week-old infants, respectively. Twenty-three cases diagnosed in the first year of life have been collected in Japan [1800].

The frequency of tumors in the two sexes is about equal.

Ependymomas can occur in any part of the ventricular system but are most common in the posterior fossa, followed by a supratentorial location, the spinal cord and the cauda equina. The ratio between infra- and supratentorial tumors varies according to the series: 70:52 [1780], 86:32 [922], 26:20 [2115], 34:14 [2324], and 30:13 [581]. In a personal series a ratio of 101:72 was found. However, while in adults the frequencies of infratentorial and spinal tumors are similar (30% and 32%, respectively), followed by supratentorial (25%) and by cauda equina/filum terminale (11%), in children the infratentorial location clearly prevailed (57%), followed by the supratentorial (33%), in the first year of life [1800]. Spinal cord and cauda equina/filum terminale tumors are less frequent (3.8% and 5.7%, respectively). In children older than 5–8 years, the relative frequency is the same as in adults.

A primitive location in the pontocerebellar angle is rare; usually, tumors involving the pontocerebellar angle occur in the fourth ventricle. Ependymomas of the foramen of Monro deserve particular mention because of the hydrocephalus they cause and their particular histological problems.

Spinal intramedullary ependymomas may be found at any level, situated between the posterior columns and usually involving more than one segment. Ependymomas of the conus/cauda equina/filum terminale region form a separate group clinicoradiologically and histologically speaking.

Ependymomas may be part of neurofibromatosis or be associated with syringomyelia.

About 40 cases of ectopic, extraspinal ependymomas have been described, mainly located in the presacral region or posterior to the sacral bone [2309]. The most widely accepted theory is that they derive from ectopic remnants of ependymal cells [64].

In posterior fossa, the most common symptoms are nausea, vomiting, and headache, and these are related to hydrocephalus. Ataxia, visual disturbances, and other symptoms follow. In children, lethargy is very common. Papilloedema is also a frequent sign, followed by nystagmus, ataxia, and gaze palsy. Supratentorial ependymomas are characterized by symptoms of mass effect, intracranial hypertension, and focal neurologic deficit.

### 11.1.3

#### Macroscopic Appearance and Imaging

Even if they maintain a close relationship with the ependymal covering, tumors may grow deeply into the white matter of the hemisphere or exit from the ventricular system. Their macroscopic appearance and the extent of diffusion vary depending on the site. In the fourth ventricle (Fig. 11.1), tumors usually grow from the floor as small, lobulated, grayish masses. They can fill the ventricle, exit from the foramina, and spread along the cerebral axis. One of the preferred sites for expansion is the pontocerebellar angle. The supratentorial tumors, if they grow into the ventricles, appear as grayish, intraventricular masses (Fig. 11.2). If they expand in the white matter, they acquire a grayish-red color and appear well demarcated from the nervous tissue. Sometimes they are cystic and necrotic. Of particular interest are the ependymomas of the foramen of Monro. In the spinal cord, the tumor is more frequently lo-

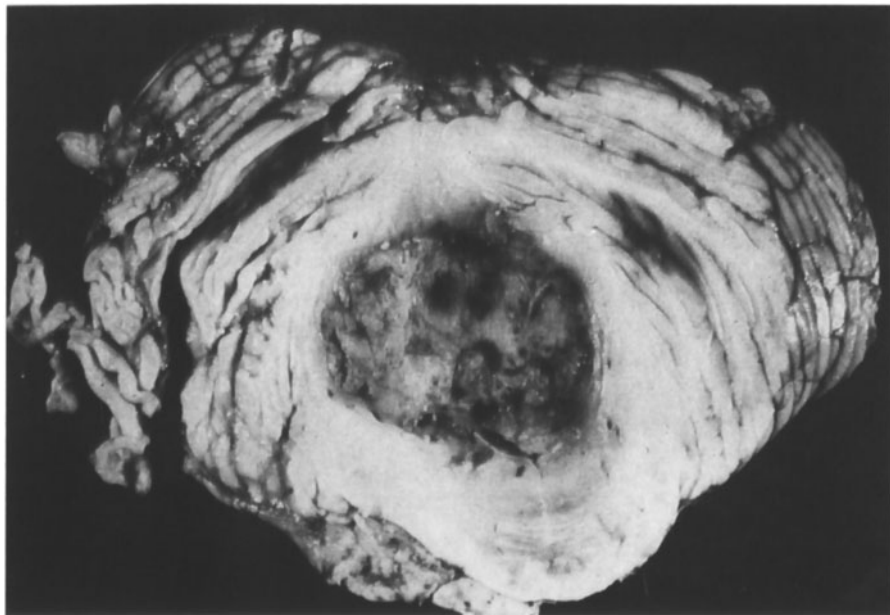


Fig. 11.1. Ependymoma of the fourth ventricle

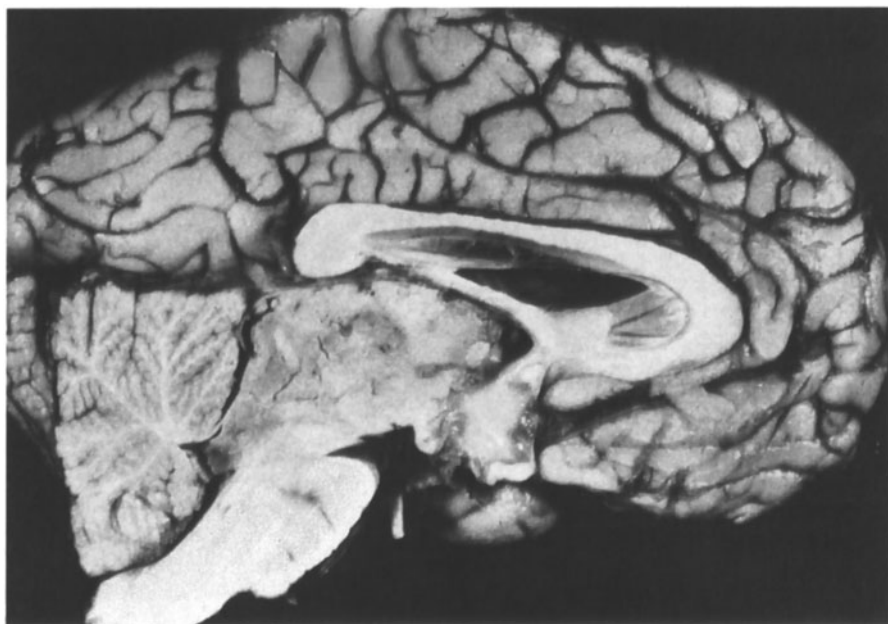


Fig. 11.2. Ependymoma of the third ventricle

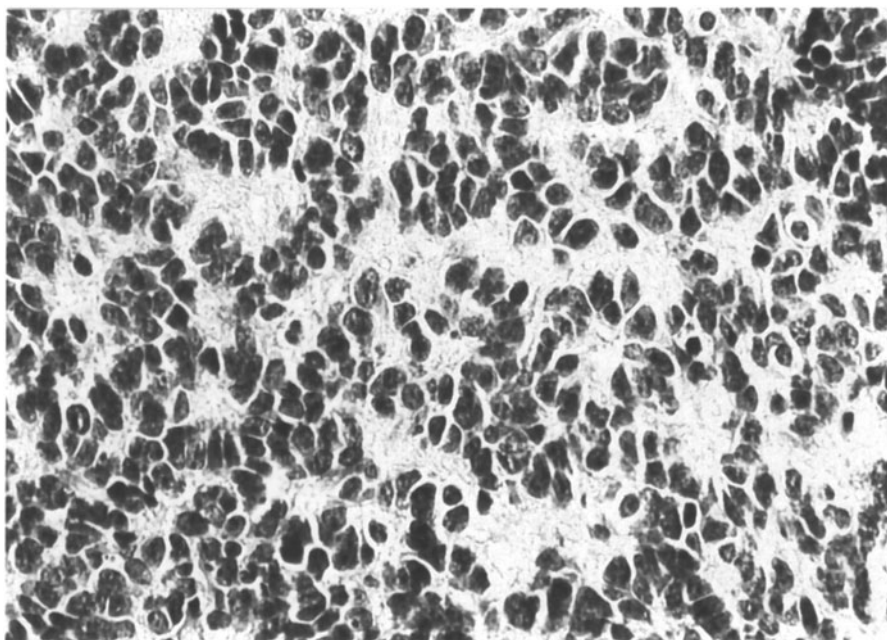


Fig. 11.3. Ependymoma, pseudorosettes. H&E,  $\times 400$

cated dorsally, lying between the posterior funiculi, being well circumscribed and extending for one or more segments.

The myxopapillary variant is typical of the cauda equina region. It arises from the conus medullaris and filum terminale. However, tumors with the classic histological aspect may also occur in this location. The tumor presents as a smooth and nodular mass which compresses and wraps around the spinal roots and other local anatomical structures. It may involve the bone and give it a “swollen” appearance. The roots may be infiltrated as well.

On computed tomography (CT) scan, the tumor may be hyperdense, isodense, or dishomogenous. It shows enhancement after contrast infusion. With magnetic resonance imaging (MRI), anatomical details are better defined and the extension of the tumor in the subarachnoidal spaces better visible. Contrast with gadolinium is mandatory.

#### 11.1.4

##### Microscopic Appearance

In the typical “cellular” ependymoma, the cells are usually isomorphous and regularly arranged without any particular pattern. Spaces devoid of nuclei, formed by cytoplasmic processes, are called “pseudorosettes” (Fig. 11.3). When processes abut upon vessels in a quite regular fashion, the so-called radiated crowns or perivascular pseudorosettes are formed (Fig. 11.4). The cells have round nuclei rich in chromatin.

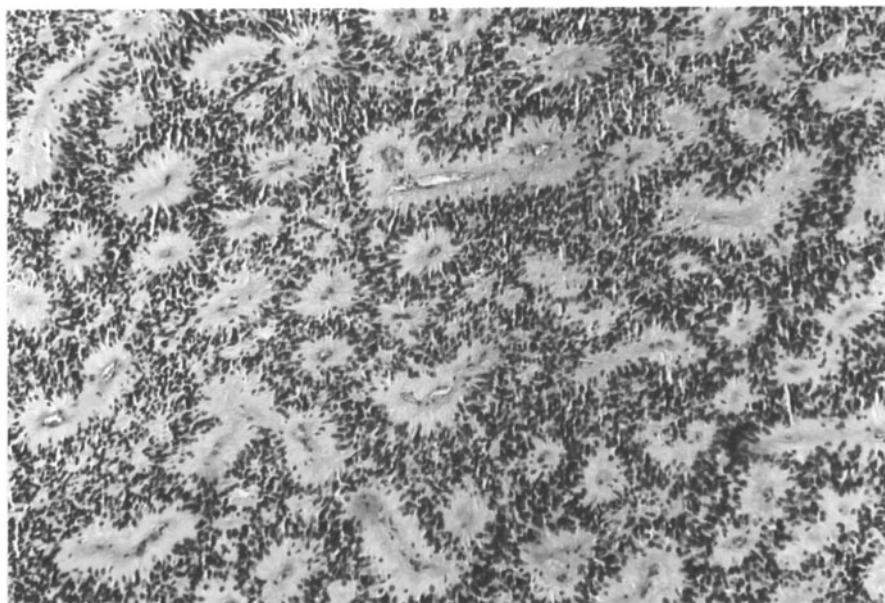


Fig. 11.4. Ependymoma, perivascular pseudorosettes. H&E,  $\times 200$

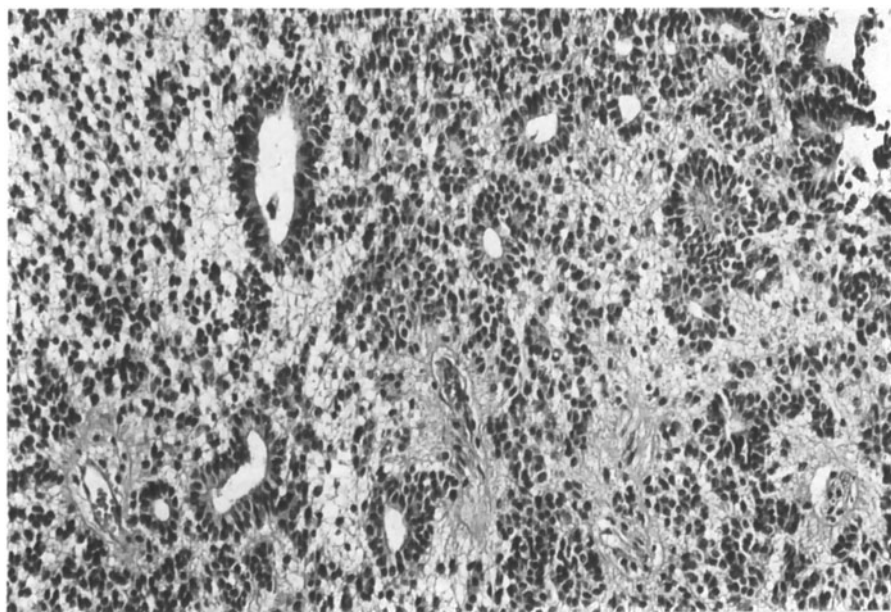


Fig. 11.5. Ependymoma, epithelial variant with canals and rosettes. H&E,  $\times 300$

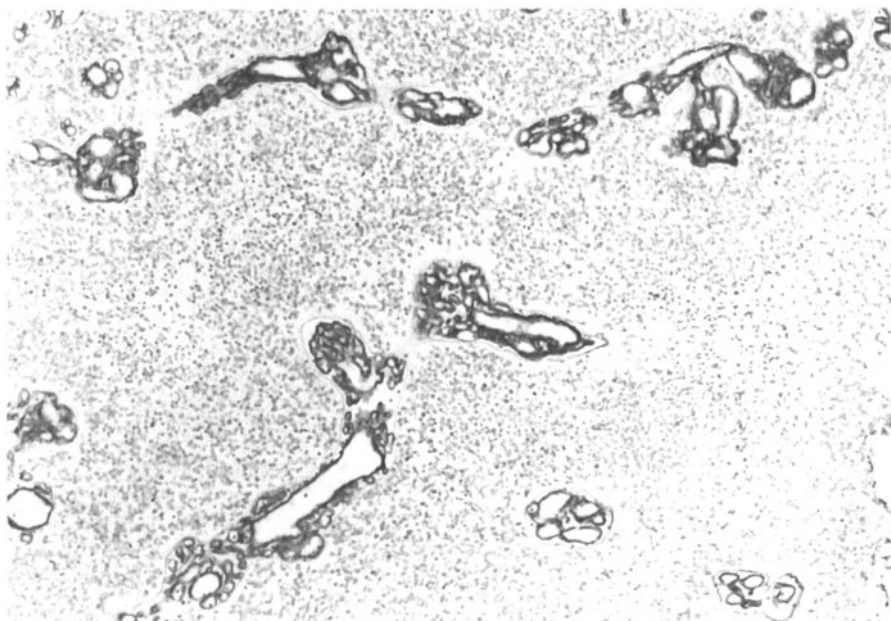


Fig. 11.6. Ependymoma, multichannel vascular structures. Laminin, PAP-DAB,  $\times 200$

The rarer “epithelial” ependymoma is characterized by ependymal rosettes, composed of columnar cells arranged around a more or less large, real lumen. The ependymal canals show the same structure, being elongated instead of spherical (Fig. 11.5). Among these formations are tumor cells without “epithelial” features. Blepharoplasts are usually thought to be characteristic of ependymoma. They are small, spherical, intracytoplasmic structures which represent the basal bodies of cilia. They are seen with phosphotungstic hematoxylin stain under oil immersion, especially if within rosettes. Their demonstration, not their absence, is important from the diagnostic point of view.

A rare papillary variant has been described, characterized by papillae which differentiate it from plexus-papilloma, because the epithelium covering their axis is multilayered, and typical structures, such as canals, are also present.

Mitoses are regularly found in variable numbers, especially in supratentorial locations. Blood vessels are numerous, often regularly distributed in groups forming multichannel, vascular structures (Fig. 11.6). Sometimes their walls are widely rearranged by thickening and hyalinization. Endothelial hyperplasia may occur up to the formation of glomeruloid structures (Fig. 11.7). In some tumors, the stromal component is particularly abundant and active, and in others the number of vessels may be extremely high.

At the periphery of the tumors and in the peritumoral tissue, intensely GFAP-positive reactive astrocytes may be found.

Cell density, sometimes very high in circumscribed areas, nuclear polymorphism, number of mitoses, and endothelial proliferation vary greatly from one tumor area to

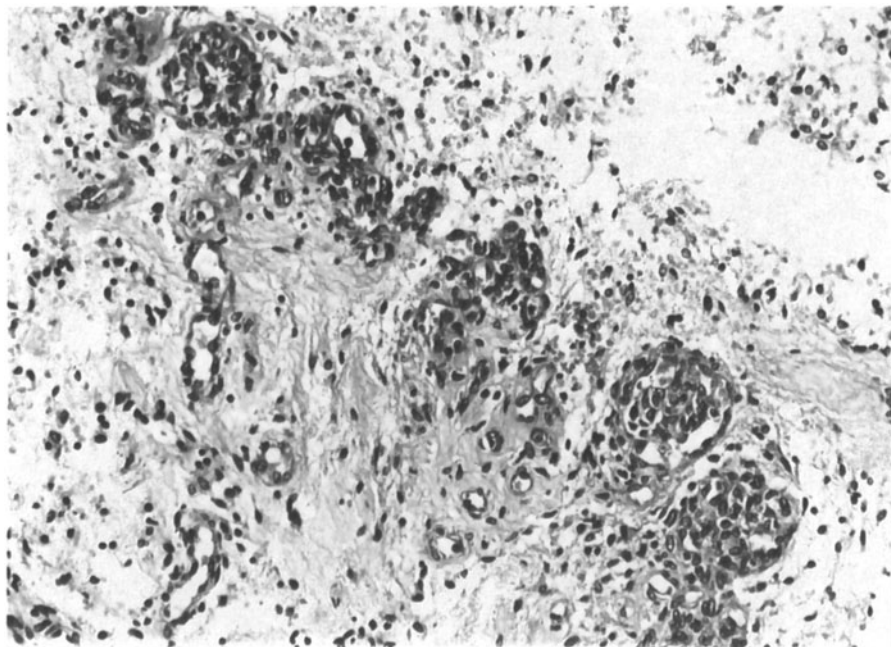


Fig. 11.7. Ependymoma, endothelial hyperplasia of glomeruloid aspect. H&E,  $\times 300$

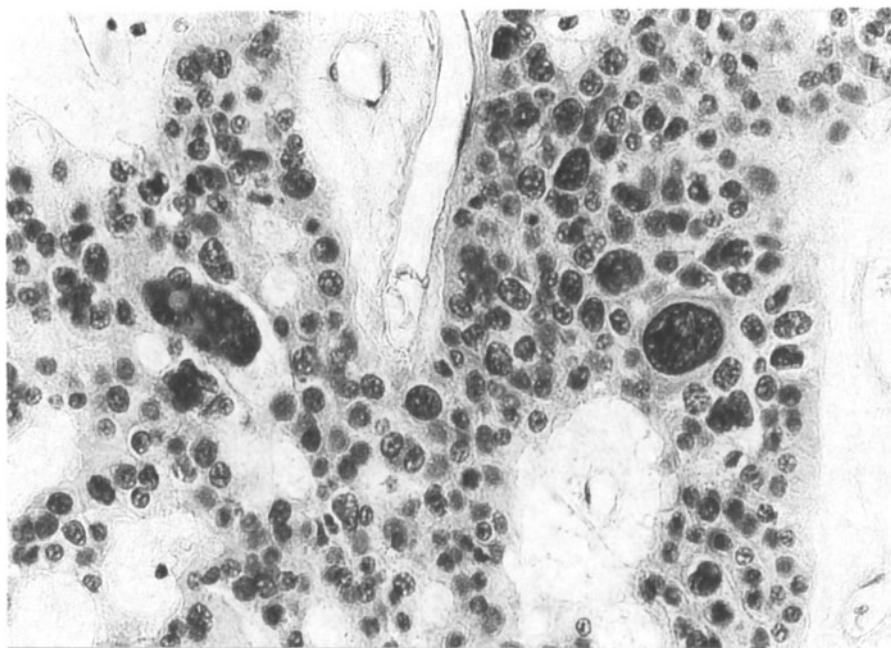


Fig. 11.8. Ependymoma, nuclear polymorphism. H&E,  $\times 1000$

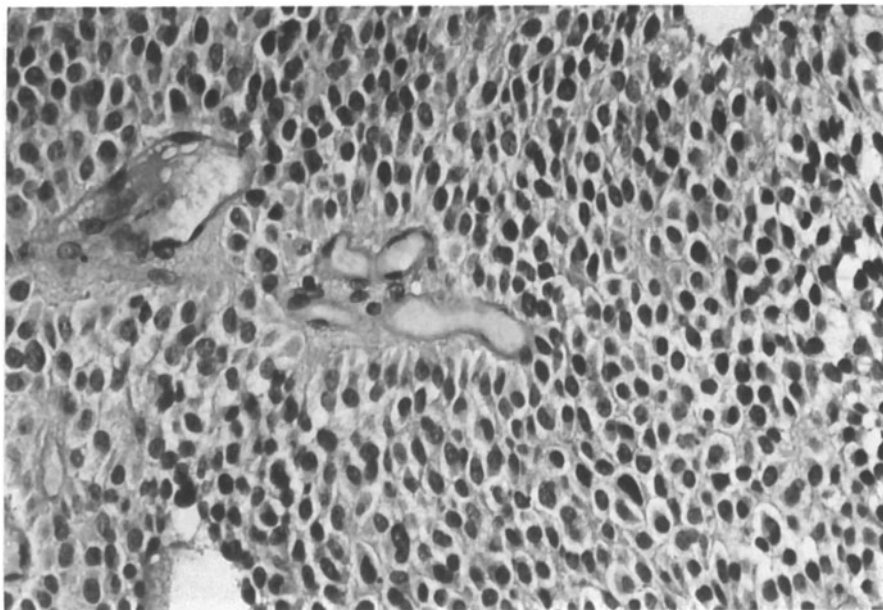


Fig. 11.9. Ependymoma, clear cell tumor. H&E,  $\times 400$

another. Nuclear polymorphism may reach the aspect of monstrous nuclei, and round nuclear inclusions are quite frequent (Fig. 11.8).

The various cellular features, epithelial and pseudopapillary, as will be said later, can coexist even if with site predilections. For example, the epithelial features are more frequent in the spinal cord. Subependymomatous areas may be present, especially when the tumor is located in the fourth ventricle. Tumors composed of ependymoma and subependymomatous areas are better classified as ependymomas [978]; they are associated with a shorter survival period than subependymomas and show a predilection for the first decade of life [2975, 1556].

#### 11.1.5

##### Regressive Events

The main regressive events are represented by necrosis, cyst formation, calcifications, and vacuolar degeneration. The cysts, especially frequent in supratentorial locations, are formed following a process of tissue liquefaction. An identical process is at the basis of the oligodendroglial-like features, present especially in ependymomas of the foramen of Monro, for which they are almost characteristic. These tumors are known as “clear cell” ependymomas (Fig. 11.9). It has been disputed for a long time whether these aspects represented a true oligodendroglial differentiation [1659, 1250] or whether they are secondary aspects [2796, 1638]. Under the electron microscope, these cells show junctional complexes, microvilli, and cilia. They are, therefore, to be considered ependymal [1620].



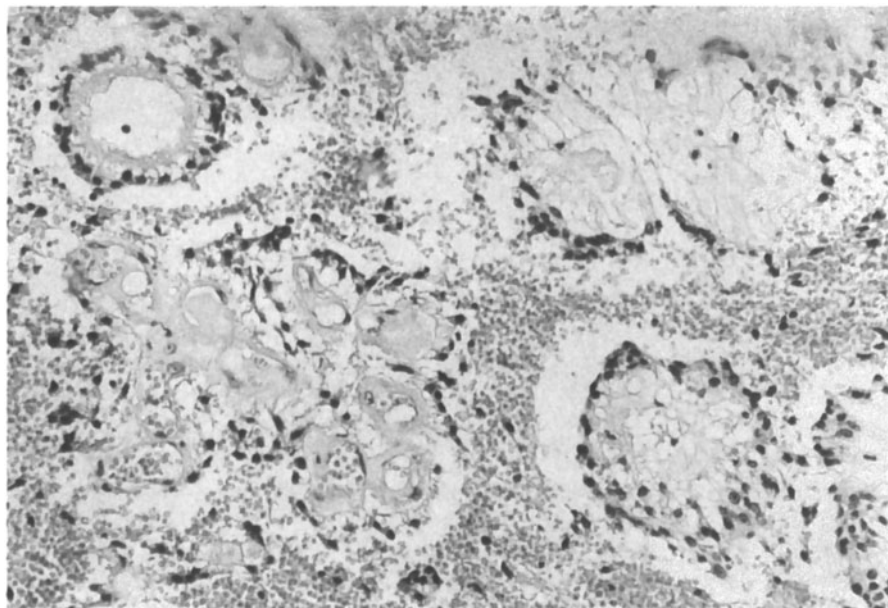


Fig. 11.10. Myxopapillary ependymoma, degeneration of the vessel walls and deformed perivascular structures. H&E,  $\times 300$

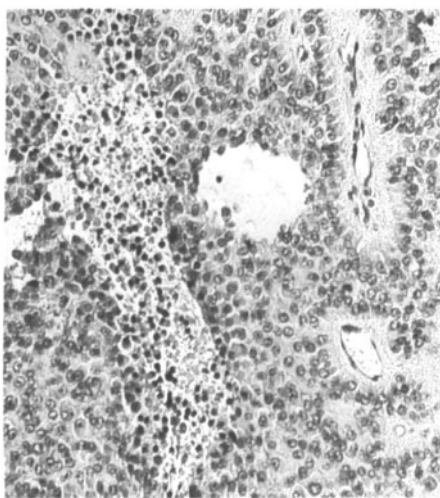
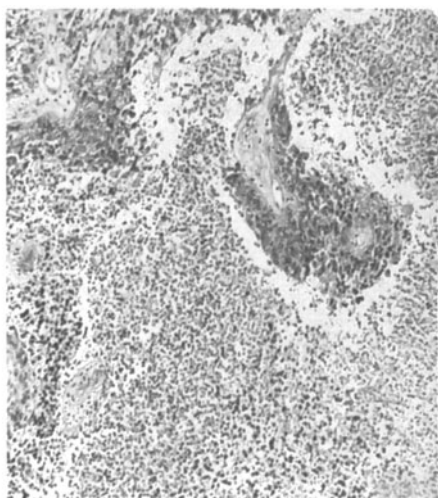


Fig. 11.11a,b. Ependymoma. a Wide necrosis. H&E,  $\times 150$ . b Small focal necrosis. H&E,  $\times 400$

The interval tissue liquefaction may give rise to tissue rarefaction with the formation of GFAP-positive stellate cellular elements. The astrocytic features, however, are not necessarily to be interpreted as secondary.

Myxomatous degeneration, present almost exclusively in spinal locations of the filum terminale, constitutes a regressive phenomenon which is fairly characteristic. It seems to be due to the effect of pressure atrophy, which causes interval cell disappearance and hyalin-mucoid degeneration of the vessel walls with the secondary formation of papillary structures. The end process is characterized by the presence of hyalin-mucoid clods, positive on mucin and alcian blue staining, bordered by a thin crown of cuboid or columnar cells. The papilliform aspect seems to be due to swelling of the vessel wall caused by various factors, vascular, mechanical, and so forth, peculiar to the location. Radiating crowns are widely modified: Either the processes are no longer visible because of the swelling of the vessel walls, or they are very long (Fig. 11.10). The myxopapillary ependymoma is not, therefore, a type per se, but a type of cellular ependymoma resulting from degenerative changes.

The various regressive events mostly involve the parenchyma away from blood vessels. They may lead to the formation of pseudopapillae resulting from intervascular degeneration with preservation of the cells, forming perivascular crowns. This mechanism is at the basis of the pseudopapillary variety of ependymoma.

Particularly frequent in this tumor are calcifications, which are sometimes also visible radiologically. In fact, they have been observed on X-radiographs in 30%–40% of cases [427]. Histologically, they are found in 20%–50% of cases [897, 3349, 2131, 2988].

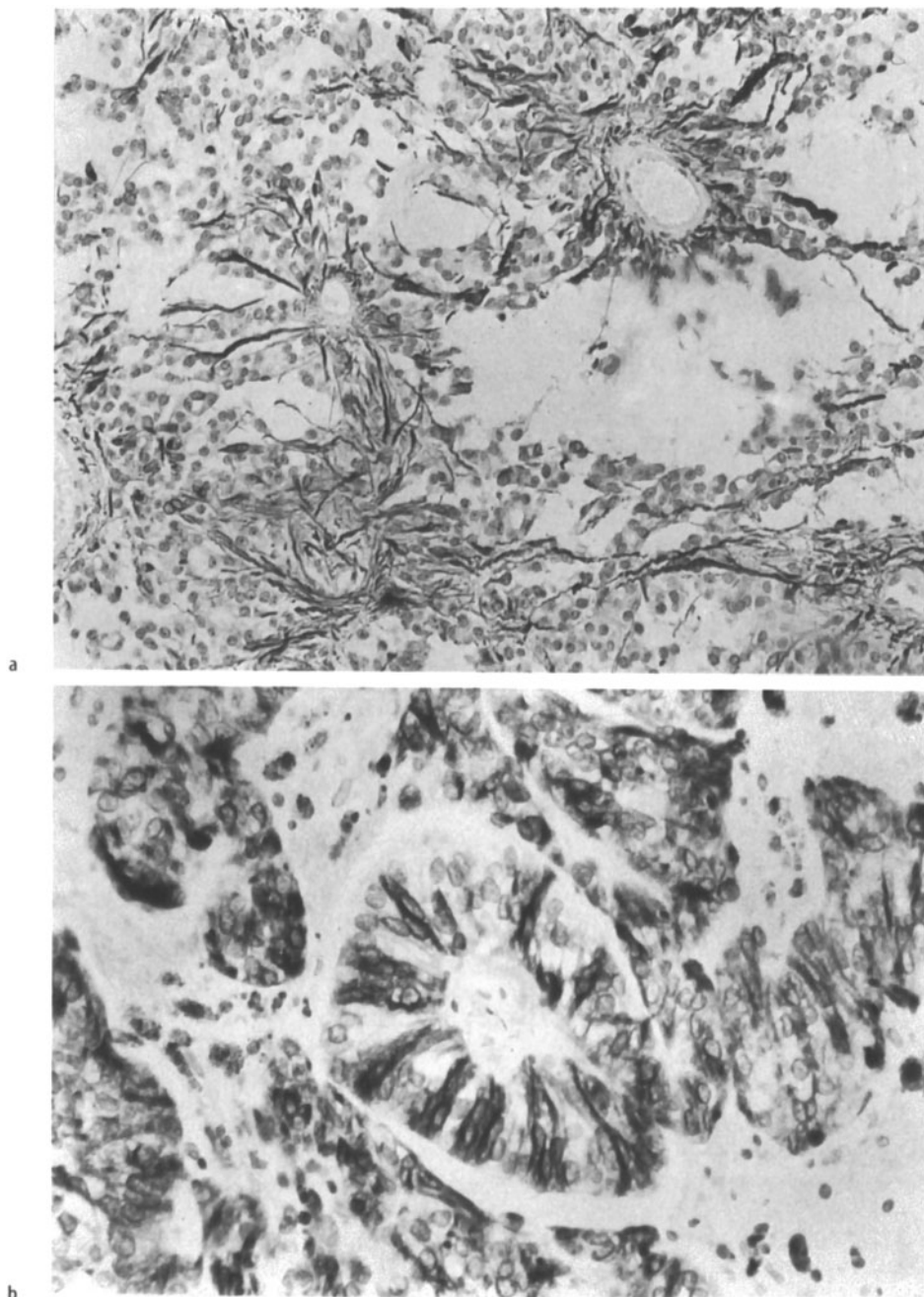
Necroses are very frequent. They may appear circumscribed necroses with pseudopalisadings, as in gliomas, as wide areas, or as very small spots, just composed of a few necrotic cells (cellular necrosis) (Fig. 11.11).

Positive correlations exist between site, age, and histological appearance. In supratentorial tumors of adults, for example, mitoses (more than five per ten high-power field, HPF), the anaplastic variant, oligodendroglial features, and endothelial proliferations prevail. In infratentorial locations, the same oligodendroglial features and perivascular infiltrates are more common. In spinal tumors, few mitoses (less than five per ten HPF), low cell density, and myxopapillary appearance are more frequent. In children, subependymomatous features in ependymomas and subependymomas occur in the infratentorial location. In relation to age, it is useful to remember that tumors occurring in infants under 1 year old are more often of the anaplastic variety, have mitotic activity (more than five per ten HPF), and often feature necrosis [3032].

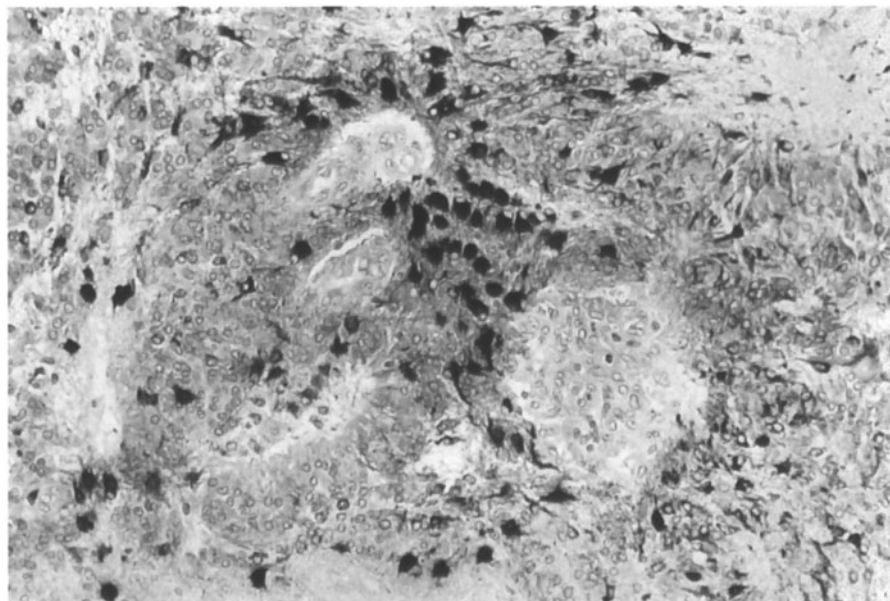
### 11.1.6

#### Immunohistochemistry

GFAP is variably positive in ependymomas (Fig. 11.12). It is strongly positive in subependymomas, underlining their astrocytic and ependymal character [3507]. In general, this is also true in cells of astrocytic origin [784], mainly in cells of perivascular pseudorosettes, elongated and with “carrot”-shaped processes (Fig. 11.12a). In rosettes and canals, staining is usually negative in the luminal pole of the cells and posi-



**Fig. 11.12a,b.** Ependymoma. **a** Glial fibrillary acidic protein (GFAP)-positive processes in perivascular pseudorosettes. PAP-DAB,  $\times 300$ . **b** GFAP-positive cells alternate with negative ones in papillae. PAP-DAB,  $\times 400$



**Fig. 11.13.** Ependymoma, glial fibrillary acidic protein (GFAP)-positive astrocytes in the tumor. PAP-DAB,  $\times 400$

tive in the mesenchymal pole. In papillae, positive cells alternate with negative cells (Fig. 11.12b), as can be observed in tancytic derivatives of the lining of the third ventricle. Reactive astrocytes around or within the tumor, as well as the tumor astrocytes scattered in the tumor or concentrated in areas, are also GFAP-positive (Fig. 11.13). The scarce positivity of areas among vessels demonstrates that the tanycytes, possible progenitors of GFAP-positive cells according to some authors [692], only give rise to a small proportion of the cells in ependymomas [784]. Positive, multipolar astrocytes are present. They have received a special interpretation in the formal genesis of the tumor [3533].

The GFAP-positivity in ependymomas has been greatly debated. The findings that intracytoplasmic filaments are present both in normal and neoplastic ependymocytes [2622, 2903, 966], that in culture these filaments show immunologic identity with the astroglial ones [3578], and that normal adult ependymocytes, except tanycytes, do not express GFAP may mean that in tumors the ependymocytes revert to more immature stages and become capable once again of expressing GFAP [2814].

The problem of the relationships between GFAP synthesis in normal and tumor ependymocytes and astrocytes has not been fully clarified. First of all, adult ependymocytes do not contain GFAP [2040, 692, 825, 3533], although they do contain bundles of intermediate filaments [2622] which are similar to astroglial filaments and give a positive reaction for GFAP [2969, 2172]. In man, from the 15th week of gestation to birth, the ependymocytes contain GFAP which they will lose in adulthood. The appearance of GFAP when mitotic activity decreases represents a sign of differentiation [2814]. It is, therefore, possible that in tumor or reactive ependymocytes

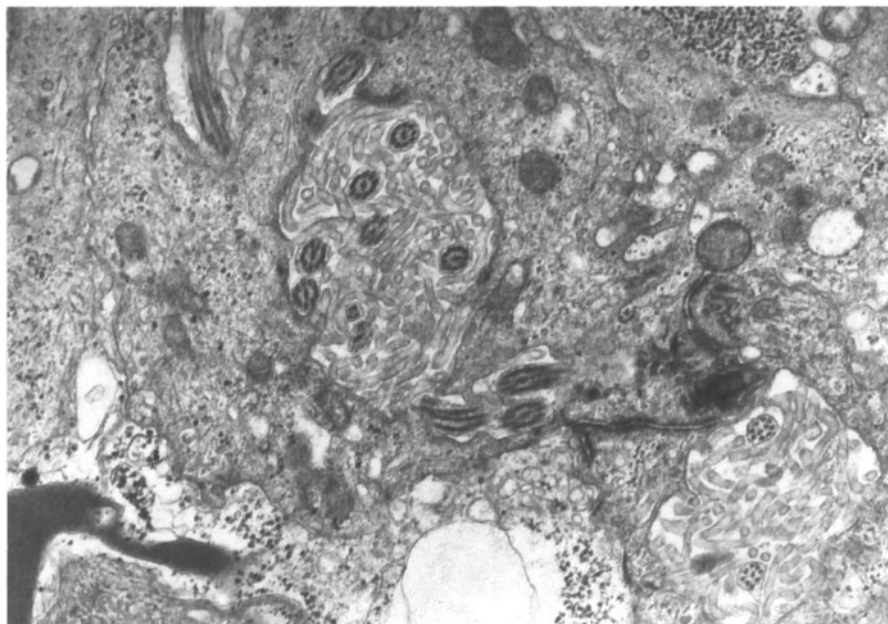


Fig. 11.14. Ependymoma, typical ultrastructural features are cilia, microvilli, and tight junctions. Uranyl acetate, lead citrate stain,  $\times 32\,000$

[556], GFAP is synthesized and visible, while in normal adult ependymocytes GFAP is produced but not in such quantities as to be visible immunohistochemically. Ependymal cells might be capable of assembling more than one type of intermediate filament, as has been demonstrated in astrocytes [2535]. Tanycytes also contain GFAP during development [309], and not all become negative in adult life.

S-100 protein has the same distribution as GFAP [3367, 1680].

The application of immunohistochemical techniques brought the old problem of the transition towards plexus papilloma back to the fore. In this tumor there are foci of GFAP-positive cells, which suggest its ependymal differentiation (see plexus-papilloma), whereas in ependymomas, in contrast to previous studies [538, 2259], cyto-keratin-positivity has been reported [2095]. Also, this finding would be indicative of transition.

#### 11.1.7

##### Electron Microscopy

In general, the ultrastructural characteristics of ependymoma cells are those of normal ependyma [3412, 332], i.e., the presence of cilia and microvilli on the luminal surface, junctional complexes on the lateral surfaces of the cytoplasm, and no basement membrane on the internal surface (Fig. 11.14) [1325]. Junctional complexes have a slit-like shape, with a 200-Å space between the cytoplasmic membranes and

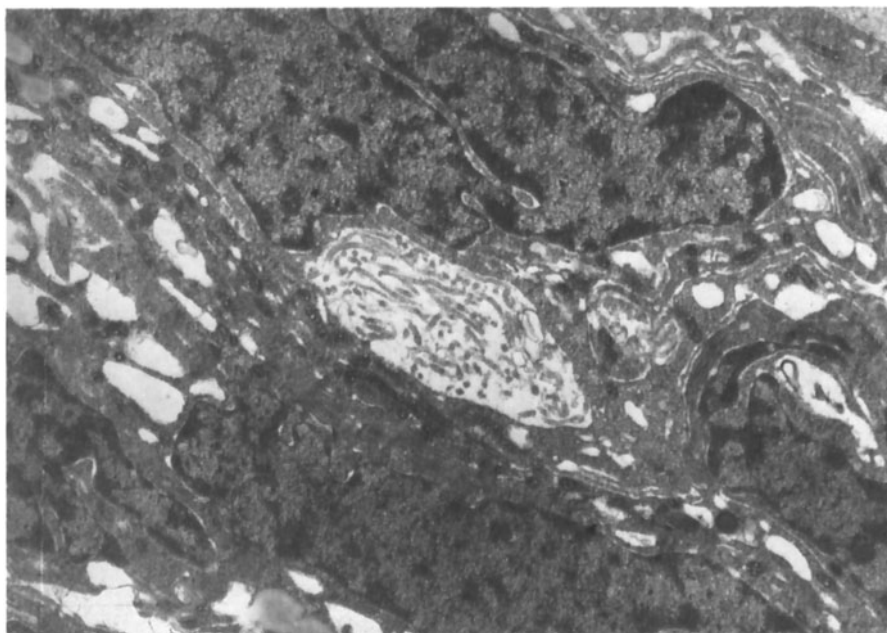


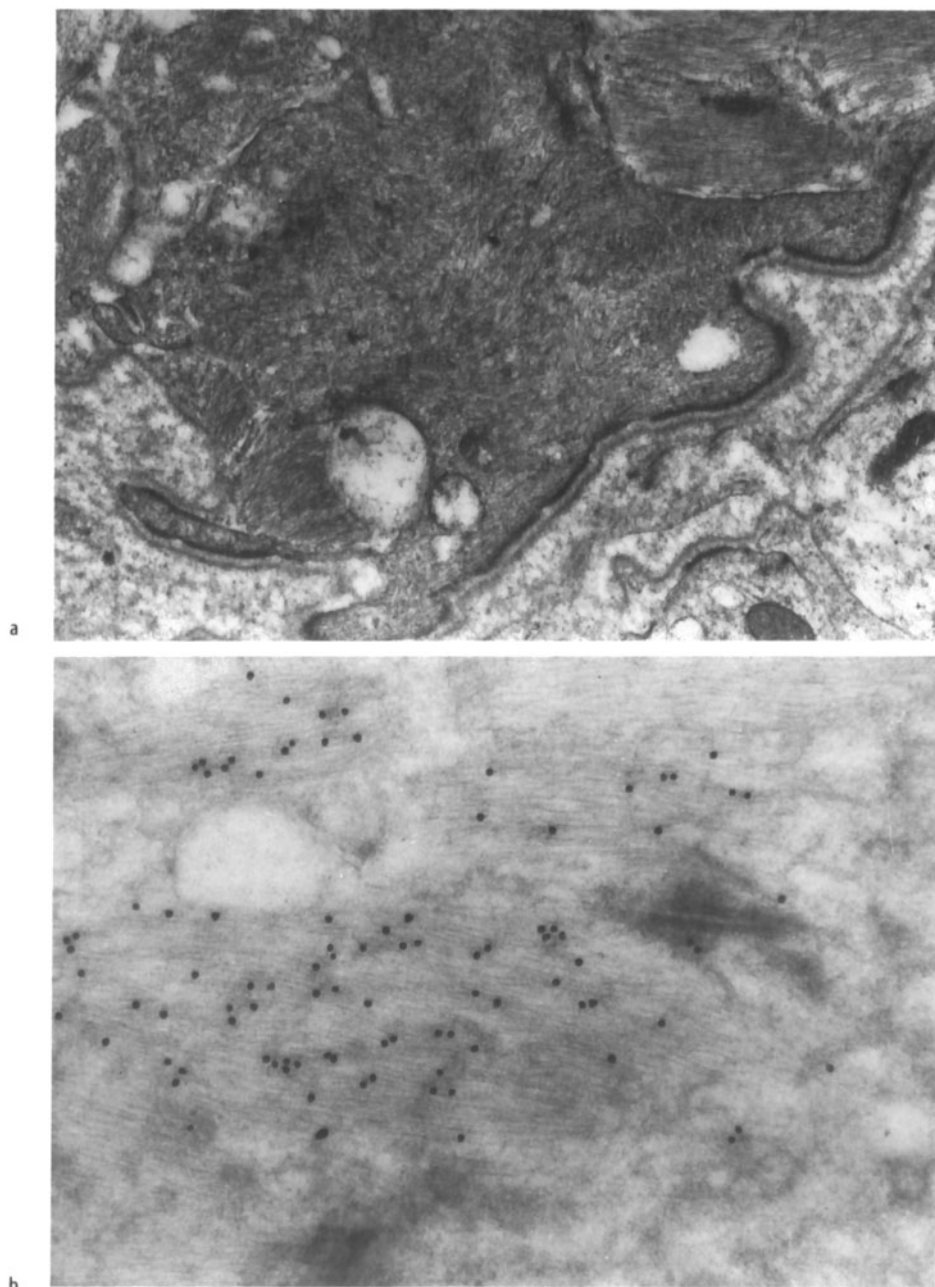
Fig. 11.15. Ependymoma, microrosette. Uranyl acetate, lead citrate stain,  $\times 20\,000$

with the zonula adherens located in proximity to the microvilli abutting upon a dilated extracellular space. The segments of these membranes are parallel and dense, with condensation of the adjacent cytoplasm. More rarely, zonulae occludentes with an internal space of  $100\text{ \AA}$  are found near the junctional complex. All these formations are found in well differentiated ependymomas [3387].

The nuclei are large, the nucleoli are visible, the mitochondria are clustered, the endoplasmic reticulum and ribosomes are scarce, and only a few Golgi apparatus are found. Cilia projecting outside the cells and intracytoplasmic cilia are common. Microvilli containing filaments and tubules together with cilia project into an extracellular lumen formed by several cells. This represents a microrosette (Fig. 11.15), which has no counterpart in light microscopy [1108].

Processes can be found containing IF with or without ependymal features (junctions), which stain immunoelectron microscopically for GFAP (Fig. 11.16). They represent either the capacity of ependymoma cells to express IF or the occurrence of astrocytic processes in the tumor.

The presence of two cellular poles, one luminal and the other submesenchymal, seems to be very important [966]. The luminal poles are formed by epithelium with microvilli; the cells are joined by zonulae adherentes, with rare cilia. The submesenchymal or glial poles are formed by parallel processes shaped like a mushroom which ends on a mesenchymal vascular surface. The cytoplasm contains 70- to  $90\text{ \AA}$  filaments. At some distance from the mesenchymal surfaces, there are bundles of processes filled with glial filaments, which form the perivascular pseudorosettes. Filaments are also found in the cytoplasm, towards the luminal surface, but here they



**Fig. 11.16a,b.** Ependymoma. **a** Intermediate filaments (IF) coexist with junctional devices.  $\times 35\,000$ . **b** Immunogold staining for glial fibrillary acidic protein (GFAP) on IF associated with junctions. Uranyl acetate counterstain,  $\times 50\,000$

are less numerous. Large masses of clustered cell bodies without polarity and with astrocytic features are found. The existence of these forms recalls the problem of GFAP expression, i.e., occurrence of tumor astrocytes or gliofibrillogenesis by ependymocytes.

In the myxopapillary ependymoma of the filum terminale, the cells do not express polarity, but their junctions are of the zonulae adherentes type with a cytoplasmic thickening, a 200- to 250-Å wide space containing amorphous material, or a loose network of filaments [2743, 3267]. Extracellular spaces containing collagen fibers are delimited by cells with a basal membrane. At times, microvilli project into these spaces [2743]. Junctions of septate type, typical of the epithelium of invertebrates, have also been described [1351].

Cilia and blepharoplasts are infrequent; however, many cells have atypical cilia. The cytoplasm contains cisternae of the endoplasmic reticulum, ribosomes, mitochondria, glycogen granules and liposomes. The majority of processes contain 70- to 90-Å microfilaments and 240-Å microtubules. The basal membrane of capillaries form the internal basal membrane of the perivascular space. The behavior of the basal membranes is peculiar to myxopapillary ependymoma and, together with the paucity of cilia, relates it to the choroid plexus. In fact, in the latter, the cells are separated from the stroma by a basement membrane [743], while ependymal cells do not have a basal membrane towards the neuropil. In myxopapillary ependymoma, the ependymal cells rest on connective tissue instead of lying on the neuropil as in other regions of the CNS.

#### 11.1.8

##### **Anaplastic Ependymoma**

The ependymoma is usually thought to be a relatively “benign” tumor with rare malignant forms. Four histological grades of malignancy have been recognized [1661]. In general, a malignant ependymoma is identified because of nuclear polymorphism, high cellular density, necrosis, and endothelial proliferation, as in glioblastoma [2796, 1297]. The existence of an ependymal glioblastoma has also been discussed [1297]. This is to be identified with the ependymal spongioblastoma of Globus and Kuhlenbeck [1101].

The application of “grading” [1661] did not lead to a precise correlation between histological features and survival. It has been regarded either as useless [1780, 922, 3652] or as useful [1147, 16]. According to some, a subdivision into three grades on the basis of cell density, number of mitoses, circumscribed necroses, and endothelial proliferations would have a predictive value [3604, 85, 1505].

The malignant variant is characterized by nuclear polymorphism, giant cells, mitoses, and endothelial proliferation, but at least part of the tumor must maintain characteristics typical of ependymoma [2904]. Even by applying these criteria to define anaplastic ependymoma, various authors have found poor [2324] or barely enough correlation with survival [495].

This is not surprising if one thinks that in six out of nine series considered, the number of high grade tumors varied between 40% and 94% [3652]. Evidently, a notable uncertainty in the identification of the malignant variant does exist. The problem



is further complicated by the use of the term ependymoblastoma to indicate the malignant variant, instead of a rare tumor with peculiar features of its own [2869], as will be mentioned later.

The identification of malignant tumors has also been tried by means of DNA microdensitometric analysis [2354] and flow cytometry [1906, 3263]. Results have been equivocal, not definitive. The labeling index (LI) after *in vivo* administration of bromodeoxyuridine (BrdU) has been found to be high in three of eight tumors, but only one of the three had histological features of malignancy, though all three tumors were clinically aggressive [2382].

From what has been said, it can be deduced that there is a great uncertainty in the identification of the malignant variant of ependymoma. First of all, the prognostic significance of its histological features is still being debated. A multivariate analysis of 102 cases [1456] demonstrated that site and age, but not mitotic activity, have a prognostic significance. In the posterior fossa, the prognosis is better in adults than in children; and the presence of rosettes and subependymomatous areas indicate a poor and a good prognosis respectively. These findings, however, have not been confirmed in another series of 62 cases [2742], where the only prognostic element was the presence of microcysts in supratentorial tumors (favorable prognosis). In this series, it has to be noted that cases diagnosed as anaplastic had the same postoperative survival as classic types. Also, in a series of 15 cases diagnosed as malignant on the basis of common histological criteria, the survival was not much different from classic cases [2847].

The reason for this failure may, in part, be the limited number of cases collected in each series, taking into account the different sites of the tumors, the diverse histological features, and the distribution over a wide range of ages. In a large series of 360 cases in childhood [1074], posterior fossa tumors with benign histological features showed, paradoxically, a worse prognosis. Histological features associated with a poor prognosis are an abundance of blood vessels, endothelial hyperplasia, mitoses, calcifications, and low cell density. Histological features found in tumors with a good prognosis are astrocytic areas, high cell density, and irregular nuclei. The classic histological variants have no correlation with survival [2828]. In 16 infratentorial ependymomas of childhood, more than five mitoses per 10 HPF (40 $\times$ ), large amounts of necrosis, and complete loss of differentiation were indicative of poor prognosis; by contrast, tumors with diffuse expression of GFAP showed a good prognosis [894].

In a personal series of 298 cases, the malignant variant, diagnosed with the same histological criteria used for gliomas, does not correlate with survival. After multivariate analysis by tumor site, the number of mitoses [more than 20 per 10 HPF (40 $\times$ )], cell density, and age (under 4 years) were prognostic factors in supratentorial tumors. No prognostic factors, with the exception of subependymoma, have been found in infratentorial and other locations [3032]. Only supratentorial cases characterized by a very high cell density (Fig. 11.17) and a large number of mitoses [more than 20 per 10 HPF (40 $\times$ )] showed statistically significant shorter survival periods [3033]. A high cell density and a large number of mitoses are, on the other hand, the direct signs of malignancy, applying the concepts, today widely accepted, of tumor progression and anaplasia. In these cases, perivascular pseudorosettes are incomplete and barely recognizable (Fig. 11.18).

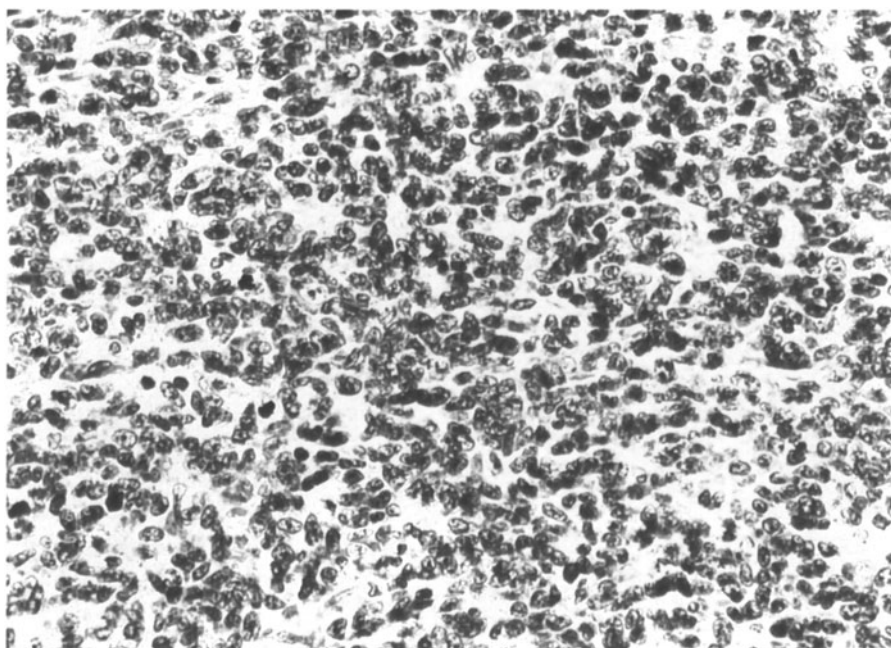


Fig. 11.17. Anaplastic ependymoma, very high cell density. H&E,  $\times 400$

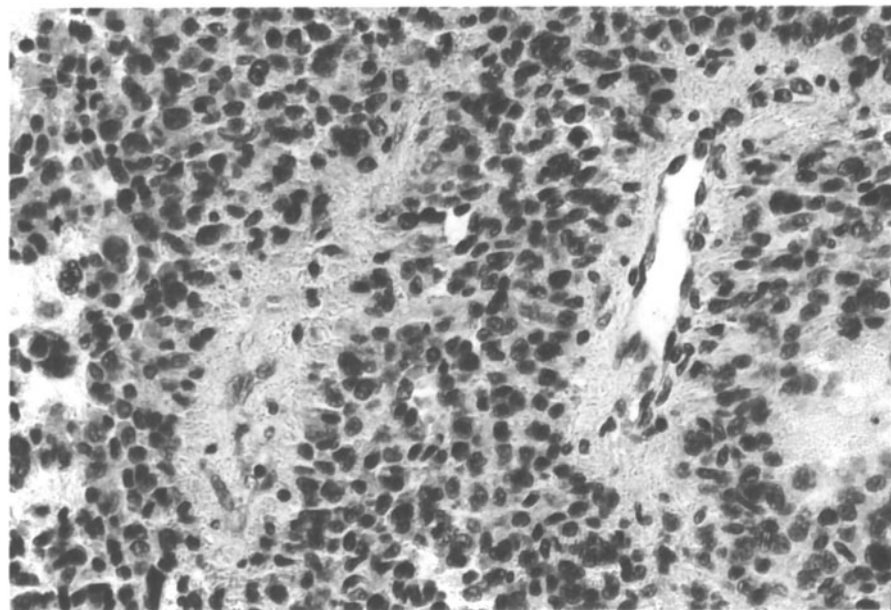


Fig. 11.18. Anaplastic ependymoma, incomplete perivascular pseudorosettes. H&E,  $\times 400$

### 11.1.9

#### Spread Via the Cerebrospinal Fluid

The frequency of spread via the CSF is extremely variable, from 0% to 60% [2916, 315, 158]. Higher percentages are obviously encountered in anatomically based series [274, 2924]. CSF dissemination is more frequent when tumors are located below the tentorium [2638, 3652] and, it seems, in the more malignant tumors [274, 2924]. It appears, therefore, that the risk of CSF dissemination is higher in malignant infratentorial tumors [1677, 2924, 1816, 547], moderate in malignant supratentorial tumors [1987, 1029], and minimal in the remainder, taking into account all the reservations which apply to the term malignant.

p53 mutations are infrequent in this tumor and do not seem to play a role in its pathogenesis and progression [901].

### 11.1.10

#### Treatment and Prognosis

Treatment of ependymomas is, in the first instance, surgical resection. Although some ependymomas may be totally removed, the 5-year survival after surgery alone is 20% [922, 2324]. Postoperative irradiation (50–60 Gy) prolongs survival up to 40%–50% at 5 years [1534, 1907]. In principle, the prognosis of intracranial tumors is clearly worse than that of tumors of the spinal cord [3187, 2324], even if the survival figures may improve by including subependymomas [1456]. Similar figures are obtained for posterior fossa tumors.

The prognosis of intracranial ependymomas is worse in children [158, 1456, 3652]. Survival rates at 3 and 5 years were 23.3% and 12.5%, respectively, 34.5% and 19.5% for benign tumors and 0% for malignant tumors [581]. In another series, survival at 5 years was 51% (without postoperative mortality), with no difference between supratentorial and infratentorial locations, but with a worse prognosis in children under 2 years of age [2638]. In the first year of life the prognosis is very poor, especially for infratentorial locations [1800]. In a personal infant series, age below 2 years was a negative prognostic factor. In another series, 3- and 5-year survivors without tumor progression were 46% and 30% respectively. Positive prognostic factors were age greater than 4 years, local radiation dose of more than 45 Gy, and Caucasian race. Factors without influence on the prognosis were the amount of tumor removed, its histological grade, the radiation field, and the chemotherapy used [1128]. Tumors usually recur locally.

In a very recent series of 40 patients with intracranial ependymoma [2660], the survival rate was 57.1% at 5 years and 45.0% at 10 years; the site of progression was local, and the three significant factors after univariate and multivariate analysis were extent of resection, age, and duration of symptoms before diagnosis. The prognosis was worse in children younger than 3 years. It is very important to note the favorable course after complete or “near complete” resection. Anaplastic histological features were not significant.

There is now no doubt that radiotherapy is effective in prolonging survival, but the field size of irradiation remains a major area of controversy.

Taking into account the risk of CSF spread, craniospinal irradiation has been advocated for all high-grade tumors [2925]. However, according to some this form of treatment does not seem to ameliorate the prognosis [1128], with local relapse remaining the most significant component of failure [1129].

Routine spinal cord irradiation seems not to be useful [494, 2548].

The lack of local control of the tumor remains the main reason for therapeutic failure. Chemotherapy of both primary and recurrent tumors seems to give some positive results. VP-16, cisplatin, and carboplatin are the most commonly used drugs.

A particular problem is the spinal cord ependymoma. It is known that complete surgical removal of spinal cord tumors, using microsurgery techniques, can give excellent local control and survival rates [907, 567]. Postoperative radiotherapy is, therefore, not recommended in such cases. It is recommended, however, in cases of incomplete removal, as improved long-term survival rates at 5 and 10 years were 100% and 73% [1748], 87% and 67% [520], and 69% and 62% [3664], respectively. The recommended dose of radiotherapy is 40–45 Gy.

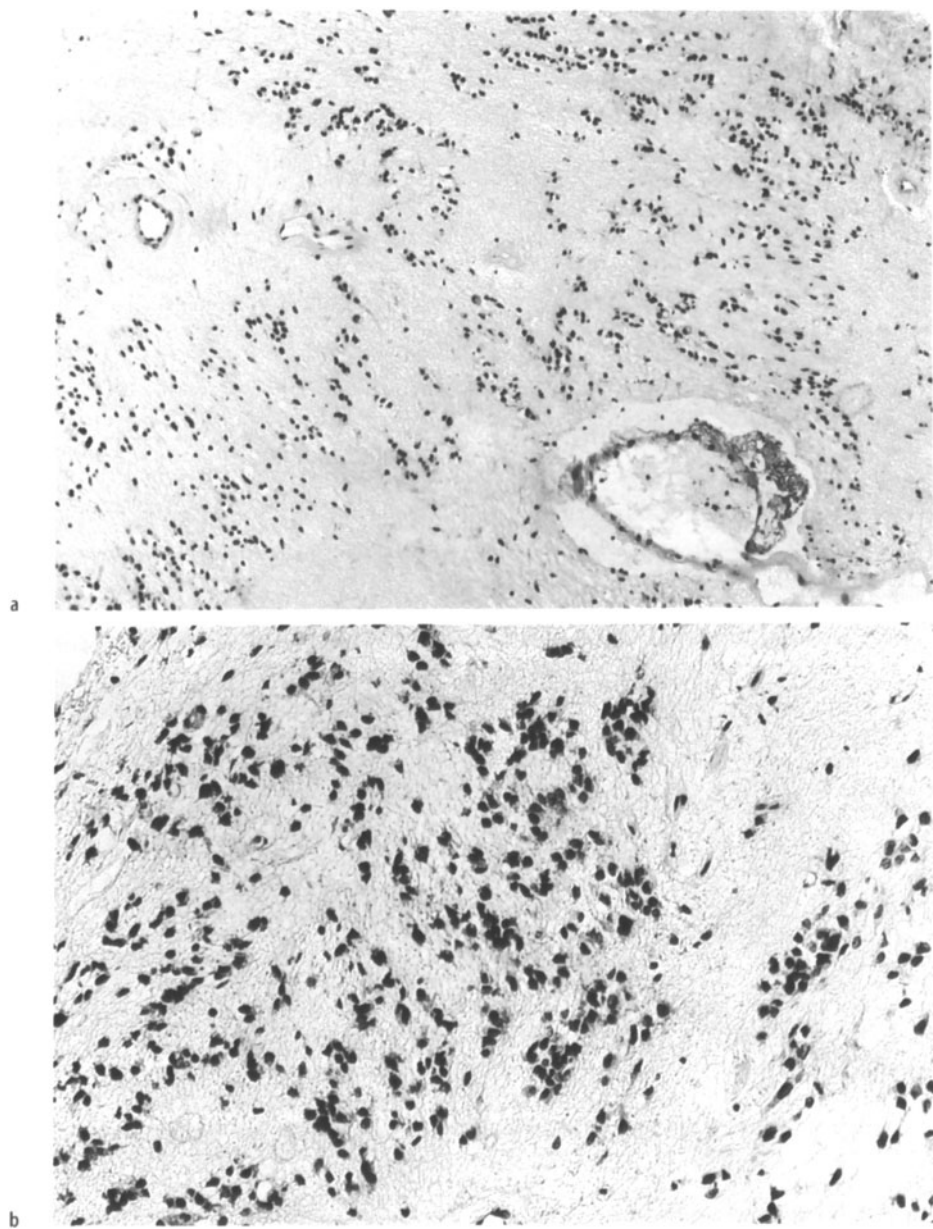
Spinal cord ependymoma may often be totally excised with a very good prognosis with long survival even when the removal is not been complete.

Myxopapillary ependymomas of the cauda equina are associated with a significantly better survival rate than tumors in other sites. They show a mean survival of 19 and 14 years, respectively, after total or partial removal [3261], and radiotherapy has been suggested only when gross tumor remains [3152]. In some cases late recurrences and distant metastases, even with a totally benign histological aspect, have been reported [2181, 2881, 2309, 658]. It is possible that late distant recurrences are due to retrograde seeding, as, for example, in the cases of Davis and Barnard [658] where the distant recurrences were in the fourth ventricle or in the anterior and posterior fossae.

## 11.2 Subependymoma

Very often, subependymoma is an asymptomatic tumor, located in close proximity to the ventricular walls, which may be accidentally found at autopsy after the fifth decade. The tumors are small, round or lobulated and localized mainly to the fourth and third ventricles, but they also occur in the lateral ventricles, septum pellucidum, aqueduct, and spinal cord [962, 320, 2930, 1996, 99]. In the fourth ventricle they originate mostly from the floor and rarely from the roof [1556]. Eight symptomatic cases have been reported [3522] in the cervical spinal cord. They are more rare in the thoracolumbar location [1185].

Asymptomatic tumors are found preferentially in the fourth ventricle. Multiple subependymomas have been described in the fourth ventricle [481] or in association with cerebellar astrocytoma [481] or with plexus-papilloma [2904]. Seven cases were originally described by Scheinker (1948) [2974], while 21 [320] and 36 [481] were reviewed from the literature. Every so often, isolated cases are reported. The term “subependymal mixed glioma” was used because of the contemporaneous presence of ependymal cells and of astrocytes [481]. Subependymoma has been described as



**Fig. 11.19a,b.** Subependymoma. **a** Clusters of cells in fibrous fields. H&E, ×150. **b** Cluster of cells with intermediate characters between astrocytes and ependymocytes. H&E, ×300

characterized by small glial cell groups of subependymal glial type, alternating with areas containing glial fibers. The tumor originates from the subependymal glia [2974]. It cannot be identified with the ependymal spongioblastoma of Globus and Kuhlenbeck [2329], because it is a benign, differentiated, and mature tumor, whereas the latter is a malignant, immature one.

Subependymoma has been considered either as an ependymoma with secondary pressure atrophy [3799] or as a tumor with inactive growth, representing an arrested stage of a benign tumor or an inert lesion, such as for example, a hamartoma [1345, 1744, 2904]. It is, however, included in the ependymoma group because of the marked variability of the astroglial component, even though in the nomenclature used by some [962], such as that of "subependymal astrocytoma," the astroglial component is considered to be fundamental.

Besides the hypothesis that these tumors originate from subependymal glia [117, 2337], other proposed origins are from astrocytes of the subependymal plate [2973, 962, 320, 1107], from ependymal cells [2904], or from a mixture of astrocytes and ependymal cells [481, 978, 2975]. The tumor has also been considered as a reactive proliferation of the subependymal glia due to hydrocephalus and chronic ependymitis [2904].

Very often, subependymomatous features are found in association with classic ependymomas.

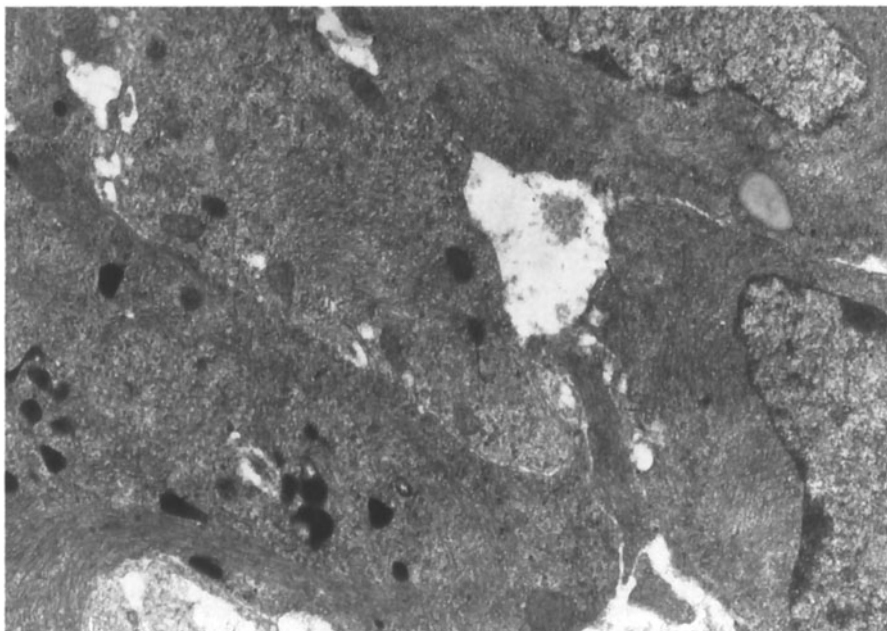
Histologically, the tumors are characterized by clusters of nuclei distributed over a thick fibrillary background formed by cell processes (Fig. 11.19). The nuclei resemble those of ependymal cells. In some cases, the processes have a clear arrangement around the blood vessels which recalls that of the ependymomatous pseudorosettes or of astroblasts. Mitoses are rare and calcifications frequent. GFAP staining is usually positive, both in the fibrous bundles and in the cells of astrocytic type [3507, 784].

Vessels are scarce, but often they appear grouped together and show endothelial proliferations, even with mitoses. Sometimes they form a wall. In one case, sarcomatous proliferation started from the vasculature of a subependymoma, forming a sarcomatous tumor [2015].

Electron microscopy demonstrates the presence of characteristics of ependymal cells [117], including blepharoplasts, but also many cells rich in IF with typical astrocytic characteristics (Fig. 11.20).

The tumor appears in all age groups. There is generally a long preoperative history, and it may be diagnosed by CT or MRI. Surgically, the tumor may be easily removed from some sites (lateral ventricles), but in others such as the fourth ventricle it is extremely difficult or impossible [1556]. In treatable cases, the prognosis is good. The tumor is histologically benign, even if nuclear polymorphism and endothelial proliferation are present. The hypothesis has been put forward that cases with more evident polymorphism and with the highest proliferative index, as judged by flow cytometry, might be more aggressive. This has not been confirmed by survival studies [2161].

Various hypotheses have been put forward to clarify the pathogenesis of this ependymoma variant. Other than the one already mentioned, some believe that the tumor represents an arrested stage of development of the ependymoma [2904]. The hamartomatous hypothesis must also be considered [1345].



**Fig. 11.20.** Subependymoma, cell processes rich in intermediate filaments (IF). Uranyl acetate, lead citrate stain,  $\times 20000$

### 11.3

#### Ependymoblastoma

The term ependymoblastoma has been and is being used to indicate the malignant or anaplastic variant of ependymoma. In reality, in the original concept of Bailey and Cushing [133], the term was used to indicate a more immature tumor deriving from the so-called ependymal spongioblasts, in contrast to the term “ependymoma” which indicated more differentiated tumors. It must be taken into account that later, in fact, the term was applied to a rare, immature, ependymal tumor, one considered to be a tumor entity [2869]. This is an embryonal-type tumor of the young, which features mitoses in the ependymal rosettes. Other cases have been described [2502, 2699, 2009, 612]. Eleven cases in the literature have been reviewed [2325].

The tumor arises in the first 5 years of life, occurring infra- and supratentorially and also in relationship with the ventricular system. It is large and circumscribed and sometimes has a necrotic-haemorrhagic appearance. In a personal collection of 298 ependymomas, there are two cases. Histologically, it is composed of trellises of crowded cells, separated by thin blood vessels. The cells are oval or elongated and poorly differentiated. Numerous mitoses are present. Perivascular pseudorosettes are not present, but there are numerous ependymal rosettes and tubules. The rosettes are formed by multiple layers and feature luminal mitoses. They resemble the Flexner–Wintersteiner rosettes of retinoblastoma and are distinguished from the rosettes of an ependymoma because the latter are not multilayered and have no mitoses. The in-

ternal lumen is delimited by an internal membrane. Blepharoplasts are present, but endothelial proliferation is not. The border with the nervous system may be clear-cut or ill-defined due to diffuse infiltration.

The tumors described have been variously treated and carry an average survival of 12 months.

The tumor corresponds to the time when the primitive cells delimiting the neural tube acquire distinctive characteristics of ependymal cells, with the development of cilia and blepharoplasts. Therefore, it shows ependymal differentiation but retains mitotic activity [2325].

In the classification proposed by Rorke (1983) [2827], the ependymoblastoma is considered to be a primitive neuroectodermal tumor (PNET) with ependymal differentiation, but in the 1991 WHO classification [1702], it is considered an embryonal tumor.

A congenital case in the sacrococcygeal region in a neonate [2360] and another in the cerebellodiencephalic region [805] have been described.



## Choroid Plexus Tumors

### 12.1

#### Plexus-Papilloma

The plexus-papilloma was the subject of several reports in the last century. After much debate, it was considered to be a tumor entity separate from the ependymomas [2861, 127], put into the group of paragliomas [1393], and then reconsidered as a subgroup of ependymoma [1659, 1661]. It derives from the epithelium of the choroid plexus, which in turn represents the differentiation of primitive neuroepithelial elements which come into contact with the intraventricular folds of the primitive mesenchyme, from which the leptomeninges arise.

#### 12.1.1

##### Frequency, Age, Site and Clinical Features

The plexus papilloma is a rare tumor which is most common in childhood. It has been found to make up 0.6% [627, 3803] of all intracranial tumors. In the personal series, it represents 0.4% of all CNS tumors. It is more frequent in infancy: 3.9% [2153], 2.3% [3429], 2.9% [817], and 3% [3264]. However, the incidence in infancy may be even greater, because some tumors are not recognized in this age group.

Eighty-three plexus-papilloma tumors have been reviewed [2153], 67 from the literature, of which 48% appeared in the first decade of life and 20% within the first year of life. Of 19 cases in another series [3677], 12 occurred in subjects less than 20 years old. The age distribution curve has two peaks: one in early childhood and the other in advanced age [3799]. This second peak is due to adult tumors discovered at autopsy.

Plexus papillomas in very early age are probably congenital and relatively frequent. They have been described in children under 1 year old and even in a premature infant [2151, 3445]. There are no significant differences between the two sexes.

The most prevalent sites are the cerebral ventricles, the tumor occurring in the lateral ventricles in 50% of cases, in the fourth ventricle in 34%, and in the third ventricle in 15.3% [3515]. These figures were 40%, 44%, and 16%, respectively, in other series [2671]; in series limited to infantile tumors, they were 72%, 15%, and 10% [817].

The general impression is that tumors of the lateral ventricles are more frequent in children and those of the fourth ventricle in adults [2904].

Tumors of the lateral ventricles generally grow at the trigon region-temporal horn; those of the third ventricle anteriorly; and those of the fourth ventricle caudally

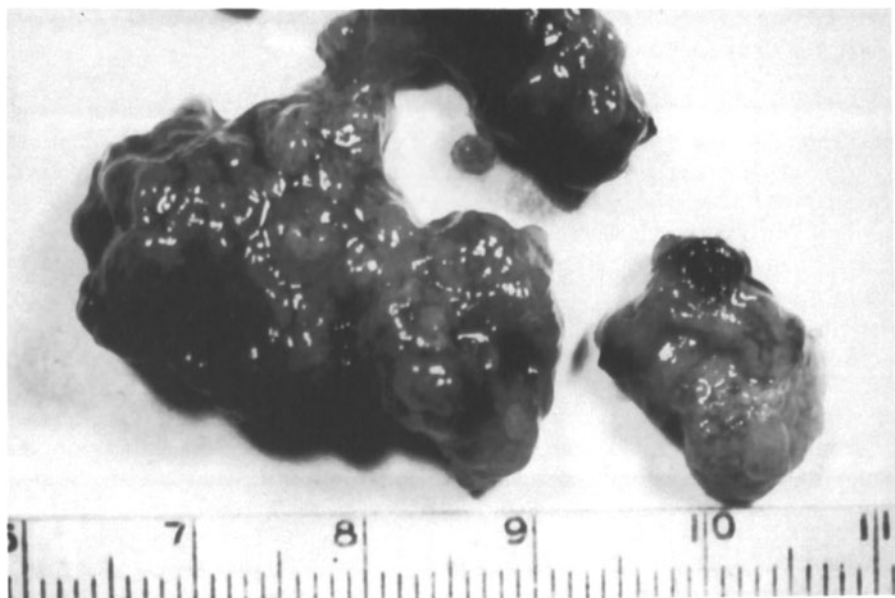


Fig. 12.1. Plexus papilloma

along the roof [3799]. Very exceptionally, the tumor is biventricular [1188, 1183]. The tumors, not rarely, may be extraventricular. This is less often due to growth from an ectopic remnant of choroid tissue [1164, 1568, 2810, 3209] and more often to a protrusion of the choroid plexus through the foramina of Luschka in the pontocerebellar angle [2312].

The most important symptoms are those involving increased intracranial pressure and, in adults, headache followed by cranial nerve palsy, visual changes, ataxia, vertigo, etc.. In children under 2 years, craniomegaly secondary to hydrocephalus is significant.

### 12.1.2

#### Macroscopic Appearance and Imaging

The tumors are globular and blue-gray, and sometimes have a cauliflower appearance (Fig. 12.1). They are soft and very vascular. The tumors grow by expanding within the ventricle first, displacing and compressing juxtaventricular structures. They may attain a considerable volume and, upon filling the ventricular cavity, exit from it and invade the nervous tissue.

In addition to hydrocephalus, on computed tomography (CT) the tumor appears as a homogeneous mass, isodense or hyperdense towards the brain parenchyma. After contrast, there is a diffuse enhancement. Calcifications may be present. On magnetic resonance imaging (MRI), the lesion appears of intermediate or increased intensity on T2-weighted images.

### 12.1.3

#### Microscopic Appearance

Histologically, the structure is very simple because, due to the presence of a large number of villi, the neoplasm maintains the picture of normal choroid plexus (Fig. 12.2a). A vascular-connective stroma forms the axes of the papillae, which are covered by a monostratified columnar or cuboidal epithelium (Fig. 12.2b). The tumor cells do not have blepharoplasts, a characteristic which distinguishes them from ependymoma. Normally there are no mitoses, but if present, they are indicative of a more aggressive behavior. Among the regressive changes, connective tissue hyalinization and calcification may occur, giving rise to the formation of psammoma bodies.

Many observations permit one to identify transitional forms between ependymoma and plexus-papilloma. During normal choroid plexus development, the neuroepithelium covers the stromal proliferations running from the leptomeninges into the primitive ventricles, resulting in the formation of papillae. There are not only histological similarities between predominantly papillary ependymomas and plexus papillomas, but also glial fibrillary acidic protein (GFAP)-positive cells in the latter. When these occur, they represent foci of ependymal differentiation [2878, 3394, 541, 2259, 741]. GFAP positivity may also be found in the normal choroid plexus. Vimentin and cytokeratin positivity have been reported in plexus carcinomas [741] and in some papillary ependymomas [2095]. Other antigens, such as epithelial membrane antigen (EMA) [741], carcinoembryonic antigen (CEA) [541], S-100 [1681], and the antigen recognized by the Leu-7-specific antibody [2613], have been identified immunohistochemically in this tumor. Transthyretin (TTR), claimed to be a specific marker of choroid plexus tumors [1300], is positive in many cases [2574, 1343]. The surface of the microvilli stains with ruthenium and, therefore, contains glycosaminoglycans (GAG) [2379]. Electron microscopy has demonstrated the occasional presence of a continuous basement membrane and junctional complexes [444, 1058, 2164].

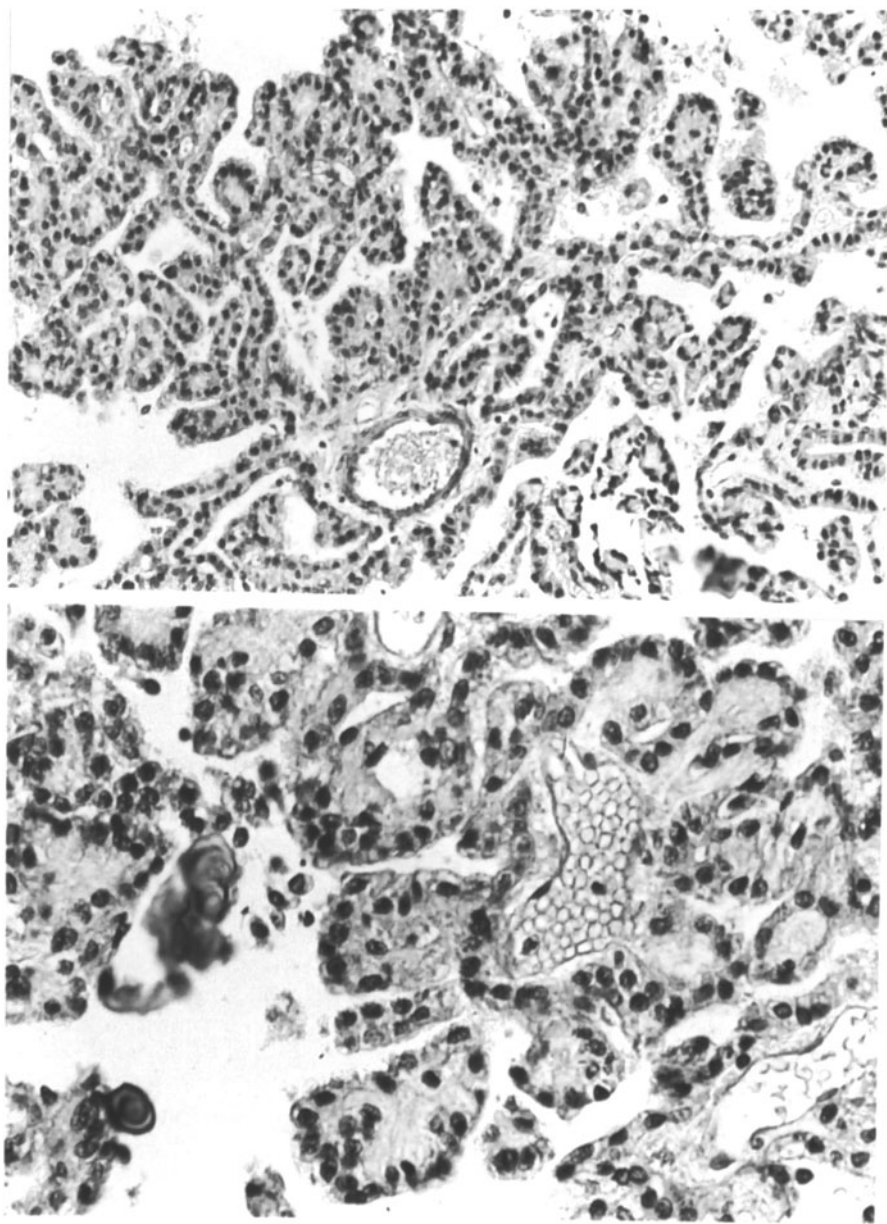
### 12.1.4

#### Treatment and Prognosis

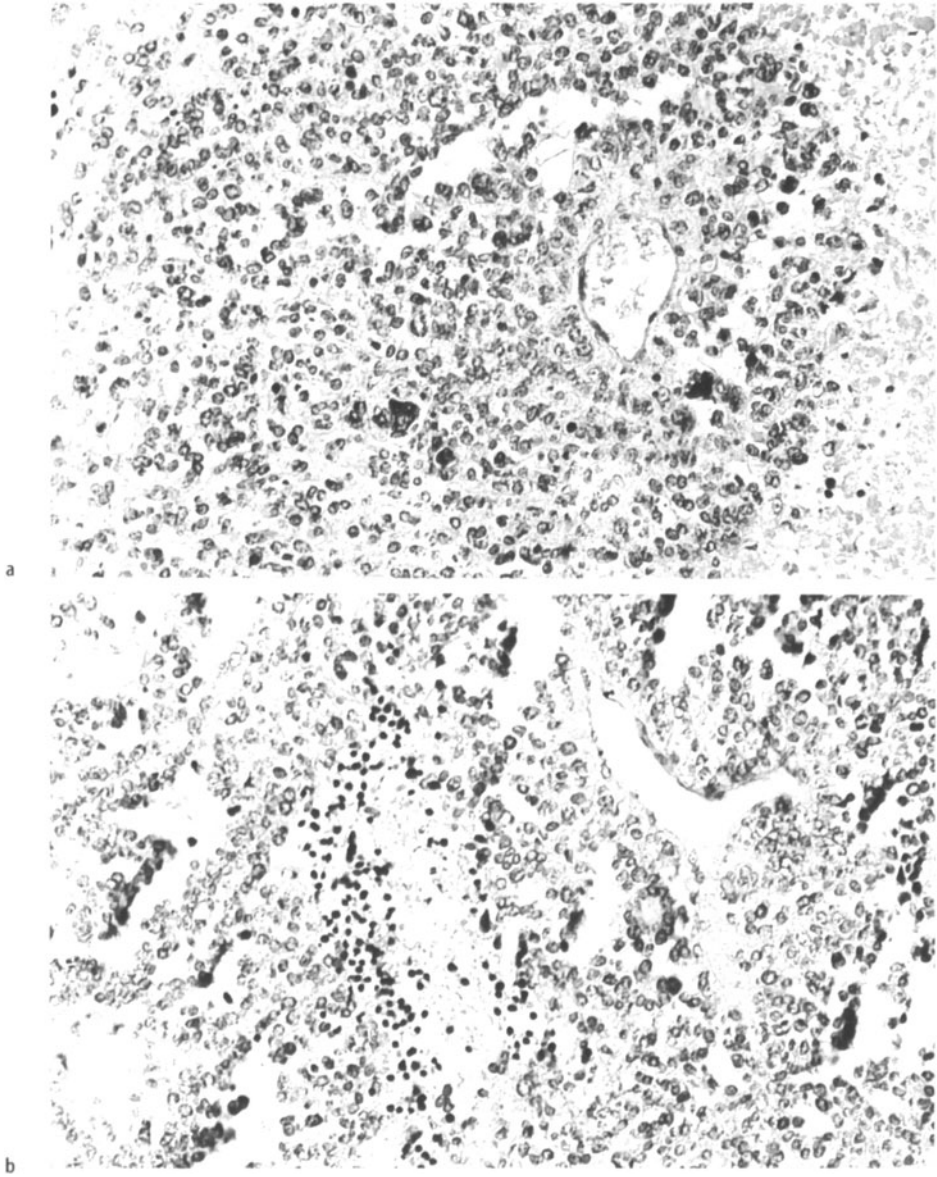
The treatment of choice is gross total resection.

The tumor carries a good prognosis, even though local recurrences are not that uncommon [2211]. Metastasis via the cerebrospinal fluid (CSF) does not take place. The associated hydrocephalus results most probably from a combination of CSF overproduction and the very high protein content, at times measured in grams, of the CSF. Surgery is very difficult technically, but today the surgery-related mortality is less than 15%. Survival at 10 years is 88% [817].

The use of radiotherapy is controversial and is usually only indicated in particular cases. Chemotherapy seems to be indicated in children with residual or recurrent tumors.



**Fig. 12.2a,b.** Plexus papilloma. **a** General architecture resembling that of choroid plexus. H&E,  $\times 200$ . **b** Structure of papillae. H&E,  $\times 400$



**Fig. 12.3a,b.** Malignant plexus papilloma. **a** Nuclear polymorphism and loss of architecture. **b** Necrosis. H&E,  $\times 300$

## 12.2

### Malignant Variant (Plexus Carcinoma)

A particular problem is represented by malignant degeneration of the plexus papilloma. Cases with the histological characteristics of plexus papilloma but with histologically malignant foci have been reported [3622, 438]. In some instances, this variant of the tumor has been called plexus carcinoma [1422, 936, 3548]. Up to 1951, 30 cases had been reported in the literature [2146]. The main problem related to nomenclature is that the term plexus carcinoma was accepted by some, but not by others. If plexus-papilloma is considered a paraglioma, it would not be correct to refer to its malignant variant as carcinoma [936]. On the other hand, the supposition that plexus carcinoma could be a metastasis to the plexus from a carcinoma of other organs has been presented [1422].

The identification of the malignant variant is difficult and essentially based on the infiltration of neural tissue, the appearance of histological signs of malignancy, the disappearance of the typical regular architecture of the tumor, and the appearance of mitotic activity (Fig. 12.3). However, it seems that the prognostic significance of these features is questionable [2211]. In the experience of others, S-100 positivity in less than 50% cells, occurrence of mitoses, absence of TTR-positive cells, brain invasion, and necrotic areas are correlated with a poor prognosis [2574].

The malignant variant is not frequent [1942] and is mostly found in children or young people [2904]. Differently from plexus-papilloma, plexus carcinoma metastasizes via the CSF [2196], though extracranial metastases have also been reported. This finding is to be considered in planning the strategy for radiotherapy. Rare malignant plexus papillomas containing melanin have been reported [177, 1855, 283]. The prognosis is generally less good than that with plexus-papilloma. Total surgical removal seems to be followed by prolonged progression-free survival, while adjuvant radiation therapy and chemotherapy are of unproven benefit [817, 2533].

In one child, minimal surgical resection followed by chemotherapy and delayed radiotherapy resulted in a survival of more than 5 years [86].

## Tumors Composed of Neural Cells

### 13.1

#### Ganglioglioma (Gangliocytoma)

Ganglioglioma is probably malformative in origin, often closely resembling a malformation. It is characterized by the presence of both neural and glial tumor cells. The frequency of neural tumor cells is very variable, ranging from tumors in which neural cells clearly prevail (gangliocytomas), to those in which they are very rare when compared with the predominant glial elements. One of the fundamental problems, especially in the latter case, is represented by the recognition of the neuronal elements. This is based, apart from the nuclear and cytoplasmic morphology (vesicular nucleus with evident nucleolus, presence of Nissl's substance, neurofibrils on silver impregnation), on electron microscopic observations (microtubules, dense or light core vesicles, synapses) and on immunohistochemical staining (demonstration of neurofilaments). In the past, many cases were mistakenly diagnosed as gangliogliomas because they contained cells with ganglioid features, as may be found in glioblastoma and other tumors.

One must recognize not only the neurons but also their neoplastic nature. This is possible when the appearance of the neurons is not so much modified by the tumor transformation as to be still recognizable. It must be considered that neurons may belong to the preexisting tissue, as often occurs at the periphery of glial tumors. Practically speaking, the presence of neurons in areas where they are normally lacking, as in the leptomeninges and white matter, or with a distribution different from that normally found, for example, in groups rather than in layers, are useful elements for the diagnosis. The recognition of the neuronal nature of the cells will be progressively more difficult as their appearance shifts towards that of neuroblasts.

#### 13.1.1

##### Frequency, Age, Site and Clinical Features

Ganglioglioma is a rare tumor. In adults, its frequency varies from 0.2% [627] to 0.4% [3803], but in children it has been reported to reach 1.7% [1030], 4.5% [3345], or even 7.6% [1543]. The tumor, in fact, is more common in the infantile or juvenile age groups, with the majority of cases occurring in patients under 30 years of age [61, 2904]. The two sexes are almost equally affected.

There are different sites of origin. The tumor more frequently occurs in the region of the tuber cinereum, in the temporal region, and in the third ventricle, but also in

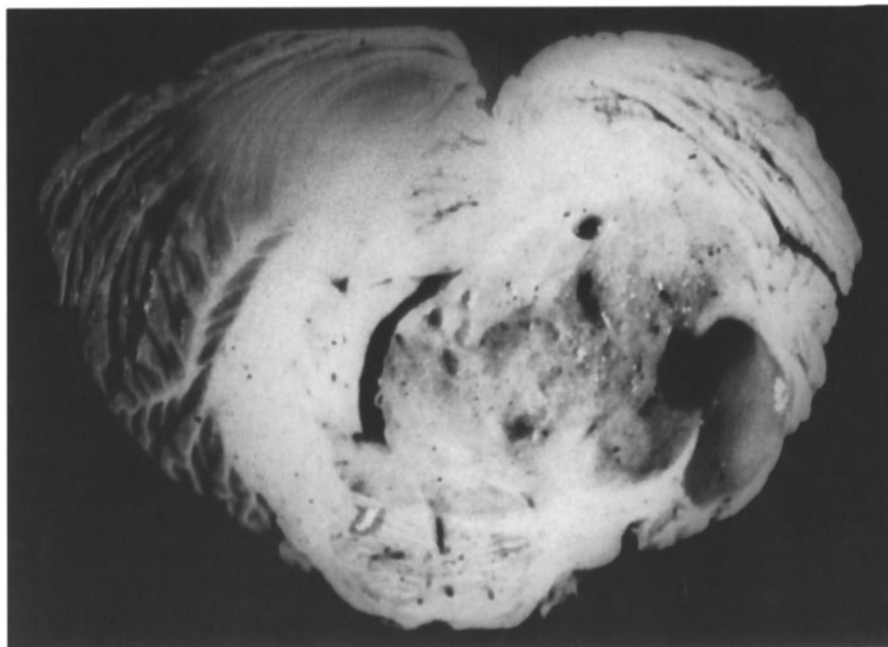


Fig. 13.1. Gangliocytoma of the cerebellum

the parietal and frontal lobes and in the cerebellum (Fig. 13.1). Other sites are less common. Cases in the pineal region have been reported [1433] (Fig. 13.2). The tumor may remain silent for a long time, revealing itself with epileptic fits or as an incidental finding during surgery for temporal epilepsy. An interesting case has been reported of an intramedullary secretory gangliocytoma in a boy developing systemic arterial hypertension during surgical manipulation of the tumor, probably due to catecholamine secretion [119].

The clinical symptomatology depends largely on the location. Epileptic seizures, present from months to years before diagnosis, are the most characteristic symptoms, especially for temporal locations. Cranial nerve palsies and hemiparesis characterize brain stem tumors.

### 13.1.2

#### Macroscopic Appearance and Imaging

The ganglioglioma is usually a small, hard, well circumscribed, grayish-pink tumor. It is often cystic (Fig. 13.1) and is sometimes calcified. More rarely, it may be diffuse.

The tumors appear on computed tomography (CT) scan as a hypodense or isodense lesions with poor contrast enhancement, sometimes cystic and frequently calcified [3778]. The cystic component is better evidenced by magnetic resonance imaging (MRI). With this procedure, tumors are hypointense on T1-weighted images



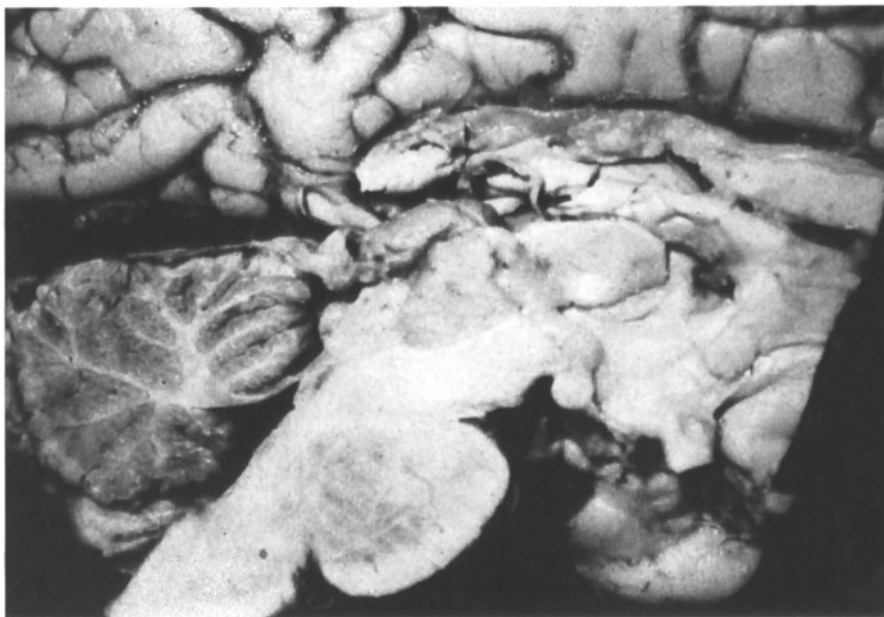


Fig. 13.2. Ganglioglioma of the pineal region

and hyperintense on T2-weighted images. Anaplastic forms appear heterogeneous on CT scan and with contrast enhancement.

### 13.1.3

#### Microscopic Appearance

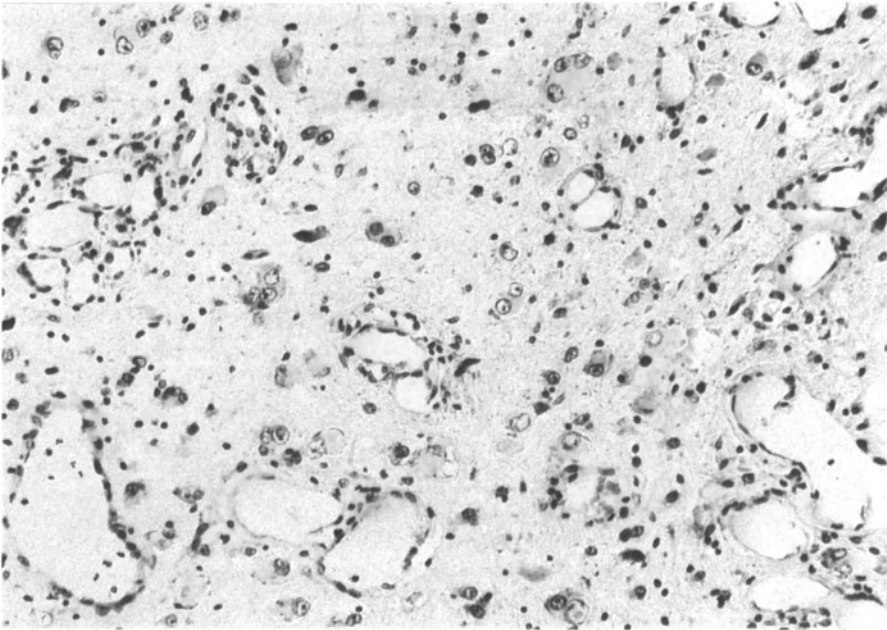
The tumor is of varied, but generally medium, cell density. It is formed of ganglion cells featuring various changes in both the cytoplasm and the processes. The cells have abnormal processes, are often bi- or multinucleated, and contain normal or irregular Nissl substance (Fig. 13.3). Smaller lymphocyte-like cells, at times interpreted as neuroblasts, may also be present. While in pure gangliocytomas the glial component is of the reactive type, in gangliogliomas the glial component is tumoral, astrocytomatous, and often with gemistocytic features.

Foci of pilocytic aspect may be found [3707], and a oligodendroglial component may be present in some cases [2681].

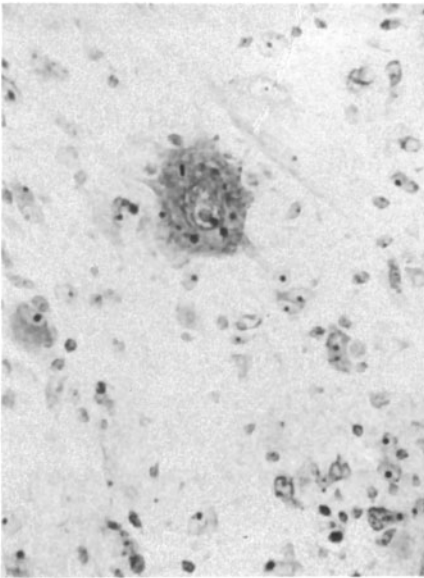
A reticulin component subdividing the tumor into lobules containing clustered ganglion cells may sometimes arise from the blood vessel stroma. Perivascular lymphocytic cuffs may be present. Exceptional cases contain neurofibrillary tangles [1386, 2466] or melanin [1433]. Among the regressive events, the formation of cysts and calcifications are most important. The tumor may extend into the subarachnoid space.

In some cases the tumors are associated with distinct glioneuronal hamartias.

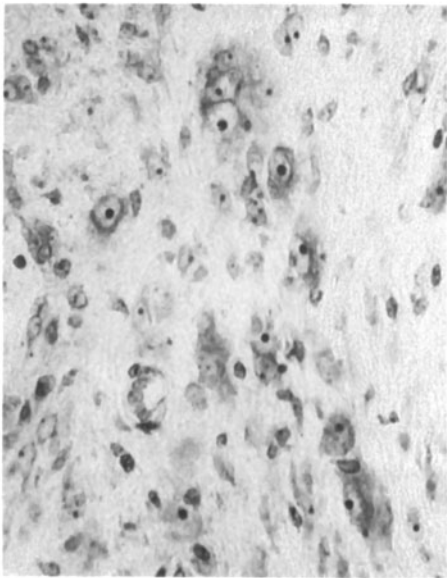
Electron microscopy can confirm the presence of neoplastic ganglion cells, with the demonstration of granules, presynaptic vesicles, and synapses [2809, 2879]. Im-



a



b



c

**Fig. 13.3a–c.** Gangliocytoma. **a** Deformed neurons and vessels. H&E,  $\times 200$ . **b,c** Binucleated neurons and Nissl grains. Cresyl violet,  $\times 400$ . (From [2994])

munohistochemically, the glial component is glial fibrillary acidic protein (GFAP) positive (Fig. 13.4b), and the neuronal one is variously positive for neurofilaments (NFs) (Fig. 13.4a) and neuron-specific enolase (NSE). In some cases, somatostatin, tyrosine hydroxylase, Met-enkephalin, Leu-enkephalin, serotonin, and substance P [3373] have been demonstrated. Yet other studies have shown positivity for vasoactive intestinal peptide (VIP) [1066]. A panel of well-characterized monoclonal antibodies (mAb) against neurofilament polypeptides, synaptophysin, and chromogranin A has been proposed for the recognition of neoplastic neurons [731].

Whereas hypothalamic gangliocytomas have been associated with endocrine dysfunctions and contain hypophysiotropic peptides, extrahypothalamic tumors are usually not associated with endocrine abnormalities. They contain neurosecretory granules and are immunohistochemically positive for peptide hormones or amines [882]. They have been suggested to derive from ectopic autonomic neural tissue.

Proliferation markers are positive only in glia cells; this is consistent with the malformative nature of the neuronal component, and labeling indices (LI) are usually very low: less than 10% for Ki-67 [3707, 2681]. This is in line with the results obtained with bromodeoxyuridine (BrdU) [1788]. p53 is immunohistochemically negative [3707].

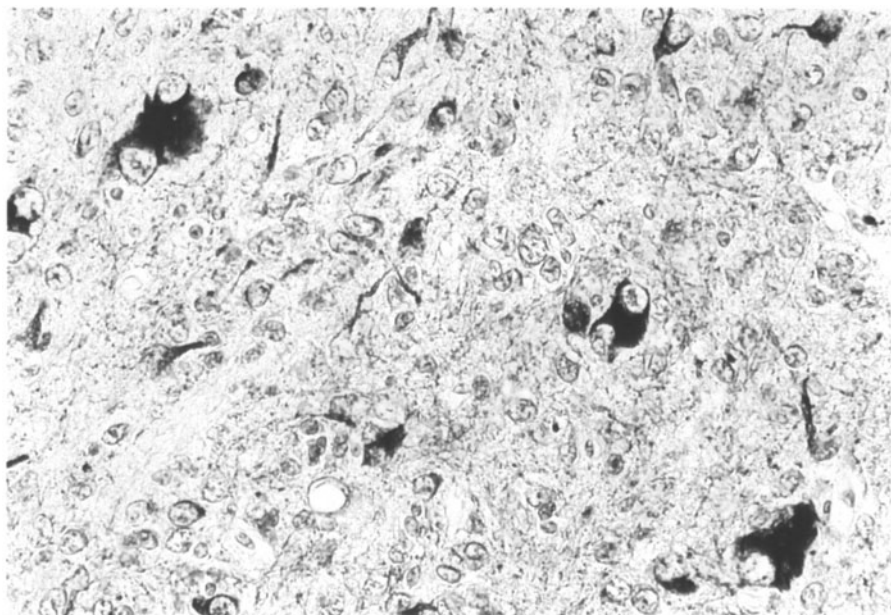
The anaplastic variant is listed in WHO classification, but its frequency is very low [492, 3778].

The origin of ganglioglioma is still controversial. In addition to a hamartomatous or maldevelopmental origin [2904, 3373, 454], an origin from ectopic neuronal cell rests derived from peripheral autonomic nervous tissue [731, 3262, 1995] has also been considered. It is also possible that the tumor derives from a single cell capable of differentiating along both glial and neuronal lines [2256]. Interestingly, some tumors can be associated with a disorganized architecture of the cortex [3707, 1515]. Cortical architectural abnormalities have been found in 50% of a series of 60 patients [2681]. There are some similarities with dysembryoplastic neuroepithelial tumors (DNT).

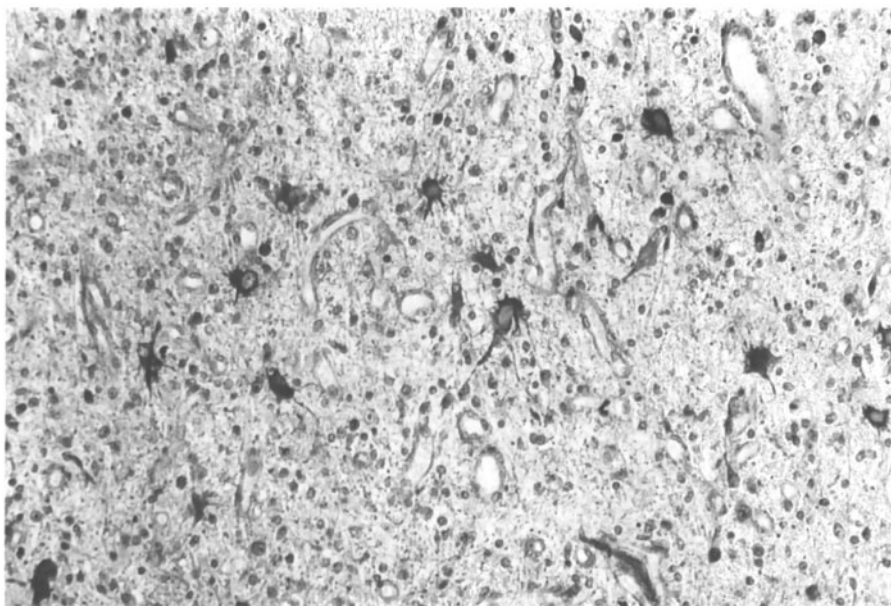
### 13.1.4

#### **Malignant Transformation (Malignant Ganglioglioma)**

A problem of notable interest is that presented by the malignant transformation of these tumors. The cases reported up to now are few. The main difficulty in the recognition of these cases is due to the fact that, if an anaplastic evolution of proliferating cells is admitted, their neuronal character would no longer be recognizable. Therefore, even if malignant forms did exist, they could not be diagnosed. In theory, it is possible to say that malignant forms, related to the presence of neuroblasts, exist, but these are best grouped with neuroblastomas having ganglion differentiation. In general, however, it is thought that anaplastic evolution occurs only in the glial component and in the glioblastomatous sense [2904]. In one case, the malignant transformation of the glial component led to a glioblastoma 25 years after biopsy [2900]. It must be emphasized that this event is quite rare. In the series of Russell and Rubinstein [2380], it occurred in ten cases.



a



b

**Fig. 13.4a,b.** Gangliocytoma. **a** Neurons shown by neurofilament (NF) immunohistochemical staining, SM31 antibody. **b** Scanty reactive astrocytes, glial fibrillary acidic protein (GFAP). PAP-DAB,  $\times 300$

### 13.1.5

#### Prognosis

As has already been stated, these lesions are akin to malformations and, in general, are considered as hamartomas, even if the possibility of progressive neoplastic transformation exists. They may be multiple or associated with other malformations such as agenesis of the corpus callosum, various ectopias, etc. The good demarcation which characterizes this tumor, especially when favorably located, permits surgical removal; thus, even though there is no known correlation between its histological appearance and the clinical course, the prognosis is, in general, good and the survival long [1543, 3192]. Recurrences are frequent, while metastases in the CNS are rare.

### 13.2

#### Dysplastic Gangliocytoma of the Cerebellum

A particular type of gangliocytoma of the cerebellum in which the dysplastic character and the affinity to a simple malformation are more evident is considered a separate lesion [1947]. It goes under different names such as dysplastic gangliocytoma, diffuse hypertrophy of the cerebellar cortex or Purkinjoma [518].

Macroscopically, it presents as a circumscribed hypertrophy of the cerebellar folia. Histological examination of the hypertrophic folia demonstrates the existence of an external layer with myelinated fibers and glial cells, a deeper layer with many small cells, and large cells resembling Purkinje cells. The central white matter is reduced or absent. According to Oppenheimer [2506], who reviewed ten published cases and reported two of his own, the "tumor" results in hypertrophy of the granular layer neurons which send fibers towards the pial surface. This finding has been confirmed by electron microscopy [2695, 890, 2773]. The two cases he reported were associated with ipsilateral leontiasis ossea and foci of ectopic cerebellar tissue. Other cases have been reported, each with its own peculiarities [437, 240]. The tumor is probably hamartomatous in origin. In two cases featuring hypertrophy of the entire hemisphere or of circumscribed areas, the granular layer contained embryonal cells (from which neuroblasts and immature ganglion cells arose) which sent axons into the thickened molecular layer. The white matter practically disappeared.

Reviewing cases from the literature, Hallervorden [1225] thought that the majority represented malformative lesions in which the hypertrophy of the internal granular layer is secondary to the malformation of the external granular layer. In another review, concerning 36 sporadic and two familial cases [59], associated lesions were found, especially an increase in volume of the skull and/or brain. The genesis of the tumor has also been attributed to a dysontogenetic multivalent leaflet of the median structures of the cerebellum [3481].

### 13.3

#### **Infantile Desmoplastic Ganglioglioma – Desmoplastic Infantile Astrocytoma**

After those described at Virginia University [3518], very few cases of infantile desmoplastic ganglioglioma (IDGG) have been reported [2423, 3277, 2130].

The tumor is located preferentially in the parietal regions with an important cystic component and without a definite cleavage plane towards the brain.

Microscopically, the main feature is desmoplasia. A dense reticulin-positive stroma contains and invests neuroepithelial cells and fibroblasts. The mesenchymal component may be highly variable. Neuroepithelial cells are represented by astrocytes, neural cells, and undifferentiated cells, with astrocytes being the most important component, especially in desmoplastic growth.

Astrocytes are GFAP positive, produce a basal lamina, and are of variable size and form. Neural cells are also of variable form; they are positive to immunohistochemistry of NF and synaptophysin. Double labeling and electron microscopy may be of great help. Mitoses may be found in association with primitive cells [3517].

The prognosis of patients with the lesion is variable, with a fairly long survival after treatment, which consists of surgery and radiation therapy.

Desmoplastic cerebral astrocytoma (DCA) of infancy is a well-characterized tumor. It arises in the early period of the first decade as a circumscribed mass, mainly located in the frontal and parietal lobes. It is histologically similar to IDGG, without any neuronal component. After the first description [3395], other cases have been reported [671, 2019]. Undifferentiated cells have been described with maturation phenomena occurring in those facing the stroma [116].

DCA may belong to the group of tumors with differentiation restricted to the astrocytic line; alternatively, it may still be considered a ganglioglioma, but with an unrecognizable neuronal component, [3517]. The neuronal component may go unrecognized because the tumor sample examined is limited. Neuronal differentiation is usually evidenced by immunohistochemical testing for synaptophysin, NF, and NSE, and it sometimes appears to be restricted to a few cells. Hence a problem arises that is of general interest and not limited to these tumors, i.e., whether it is legitimate to accept the existence of a neuronal line of differentiation on the basis of a few positive cells, without histological evidence of neurons. The fibrous, desmoplastic component is, of course, the most important pathological feature of these tumors.

In some cases [2585], cells arranged in a storiform pattern were described, similar to those seen in fibrous histiocytoma, making it unclear whether they represent mesenchymal differentiation or a simple fibrohistiocytic reaction.

In the recent WHO classification of brain tumors, DCA was put in the category of neuronal and mixed neuronal–glial tumors. So far, all cases have been reported in children, and these patients have had a good prognosis, but IDGG has also been described in an adult [1799] and in another case with signs of malignancy [3277]. The spectrum of “desmoplastic, supratentorial neuroepithelial tumors,” a name that has been suggested to cover all these tumors [2585], probably needs to be widened, especially since cases of desmoplastic undifferentiated neuroepithelial malignant tumors have been reported in children, with divergent differentiation, one of them even with a prominent angioblastic component [1860, 3726]. Small, undifferentiated, mitoti-

cally active cells have also been described [2423, 3277]. The need to enlarge the spectrum of these tumors is also suggested by the occurrence of Schwann cells, recognizable in the tumor only by electron microscopy [2423].

### 13.4

#### Central Neurocytoma

Under this name are included some para- and intraventricular (lateral ventricles) tumors arising in young subjects, which were previously classified as ependymomas of the foramen of Monro [3805] or as oligodendrogliomas. Several cases have been reported [2591, 3689, 3453, 446]. The tumor usually originates from the anterior wall of the third ventricle and extends into the corpus callosum and foramen of Monro, at times filling the lateral ventricle.

The tumor is composed of sheets of small, isomorphous cells with a clear cytoplasm and a perinuclear halo (Fig. 13.5). They are separated from one another by stromal septa containing capillaries and calcifications [1258]. Homer–Wright rosettes are present (Fig. 13.5). In some cases, there is a remarkable resemblance to oligodendroglioma [3689, 2438]; however, some features of neurocytomas, such as more varied nuclei, a more delicate fibrillary background with anuclear zones, and an inconspicuous vasculature permit distinction [2016]. Ultrastructurally, the cells appear to have a clear neuronal differentiation and synapses [1260]. Immunohistochemically, staining for synaptophysin, NSE, Leu-7, and NF is generally positive, whereas that for chromogranin is negative [1260]. In a series of 11 cases [3563], staining for NSE and synaptophysin was positive and on electron microscopy axons, synapses, neurosecretory granules, and microtubules were found. Two cases were also GFAP-positive. It is interesting to observe that, in two cases, there were signs of anaplasia with mitoses, necroses, and endothelial proliferations. Electron microscopy may be of help in the recognition of these tumors [3479].

In an immunohistochemical study of ten cases, positive staining for class III  $\beta$ -tubulin and microtubule-associated protein (MAP-2) was found. Many cases were positive for not phosphorylated NF, and none showed GFAP positivity [1315]. GFAP-positive astrocytes in the tumor are usually considered to be reactive cells. However, the occurrence of GFAP-positive tumor cells in intraventricular tumors has been reported [3563], and in cell cultures from two patients, elements with astroglial differentiation and GFAP positivity were observed [3654]; the nosographic position of this tumor has perhaps not yet been fully achieved.

It is undoubtedly difficult to draw a clear distinction between these tumors and central neuroblastomas. Some cases described as central neuroblastomas with a marked tendency to neuronal differentiation or with mature synapses could, in reality, have been central neurocytomas (see Sect. 15.3). In general, a neuroblastoma possesses clear Homer–Wright rosettes and affects younger patients. Neurocytoma cells appear to be intermediate between the immature cells of neuroblastoma and the mature ones of gangliocytoma.

These tumors derive from the subependymal plate of the lateral ventricles, i.e., from residual cells destined to be neurons [3563, 2016], and from gray nuclei of the septum pellucidum and the fornix [1260]. Also a spinal case has been reported [2016].

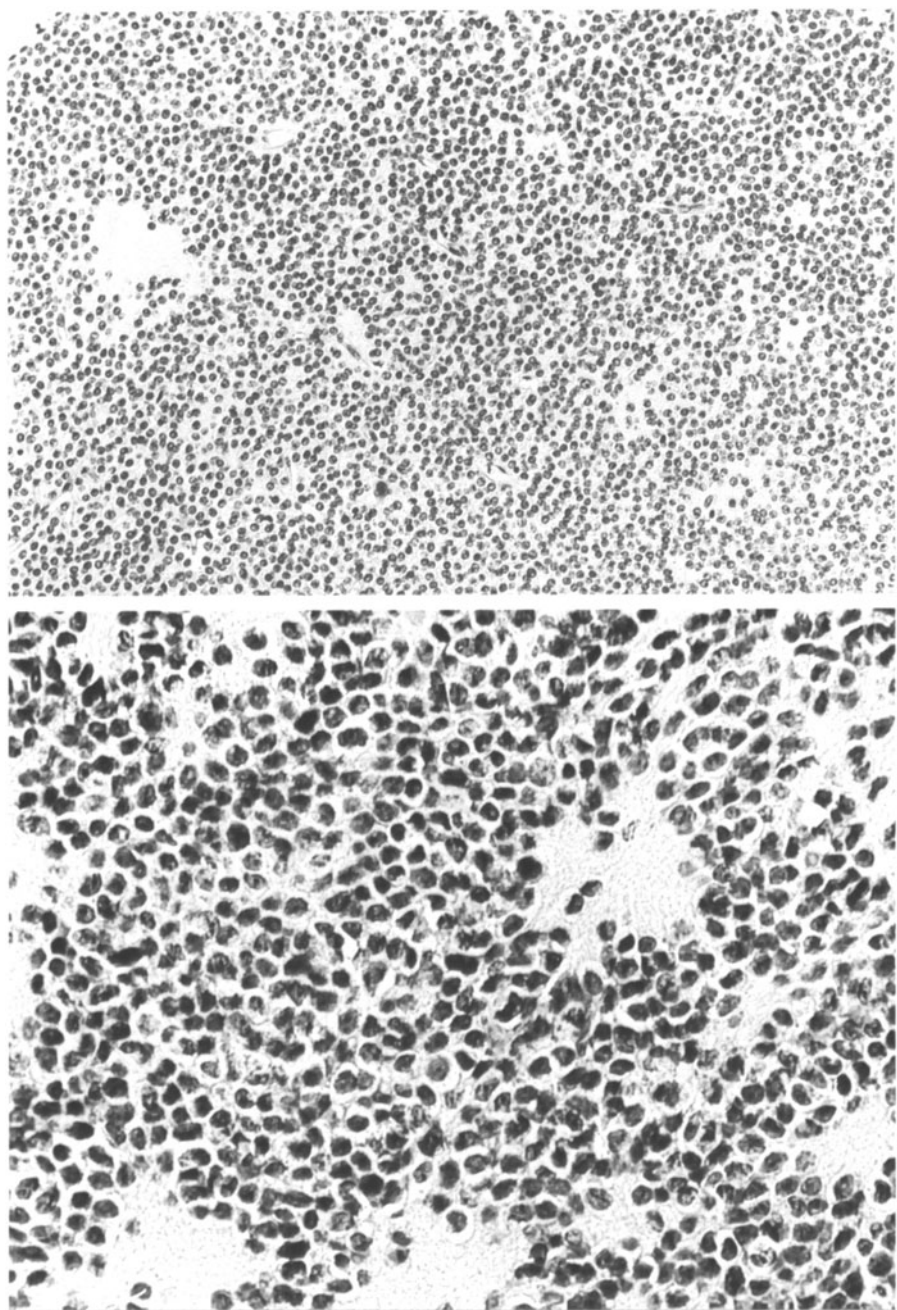


Fig. 13.5a,b. Central neurocytoma. **a** Typical architecture with “cell-free” islands. H&E,  $\times 200$ . **b** Cell halos. H&E,  $\times 400$



The tumor should be considered as a unique differentiated neuronal neoplasm, deriving from subependymal plate cells committed to a neuronal phenotype or, alternatively, from bipotential subependymal progenitor cells.

Neurocytomas follow more benign courses than neuroblastomas and may, in some cases, be cured by excision alone. Malignant courses have been reported [3747]. The role of radiotherapy is yet to be defined [21].

### 13.5

#### Dysembryoplastic Neuroepithelial Tumors

In the WHO classification, dysembryoplastic neuroepithelial tumors have been included in the category of “neuronal and mixed neuroglial tumors.” They are characterized by a critical location, multinodular composition with astrocytic, oligodendrocytic, and oligoastrocytic tumor components, focal dysplasia, and occurrence of the so-called specific glioneuronal elements. First described in 39 cases of epilepsy surgical specimens [565], they have subsequently been repeatedly reported [1252, 1141].

The frequency of the tumor is still a matter of debate. With regards to patients undergoing surgery for intractable epilepsy, the percentage was calculated as being 7.5% in the St. Anne series and even higher (14%) for other series [2744]. These tumors usually affect young patients; there were nine cases in a pediatric series of 600 patients in one institution [3396].

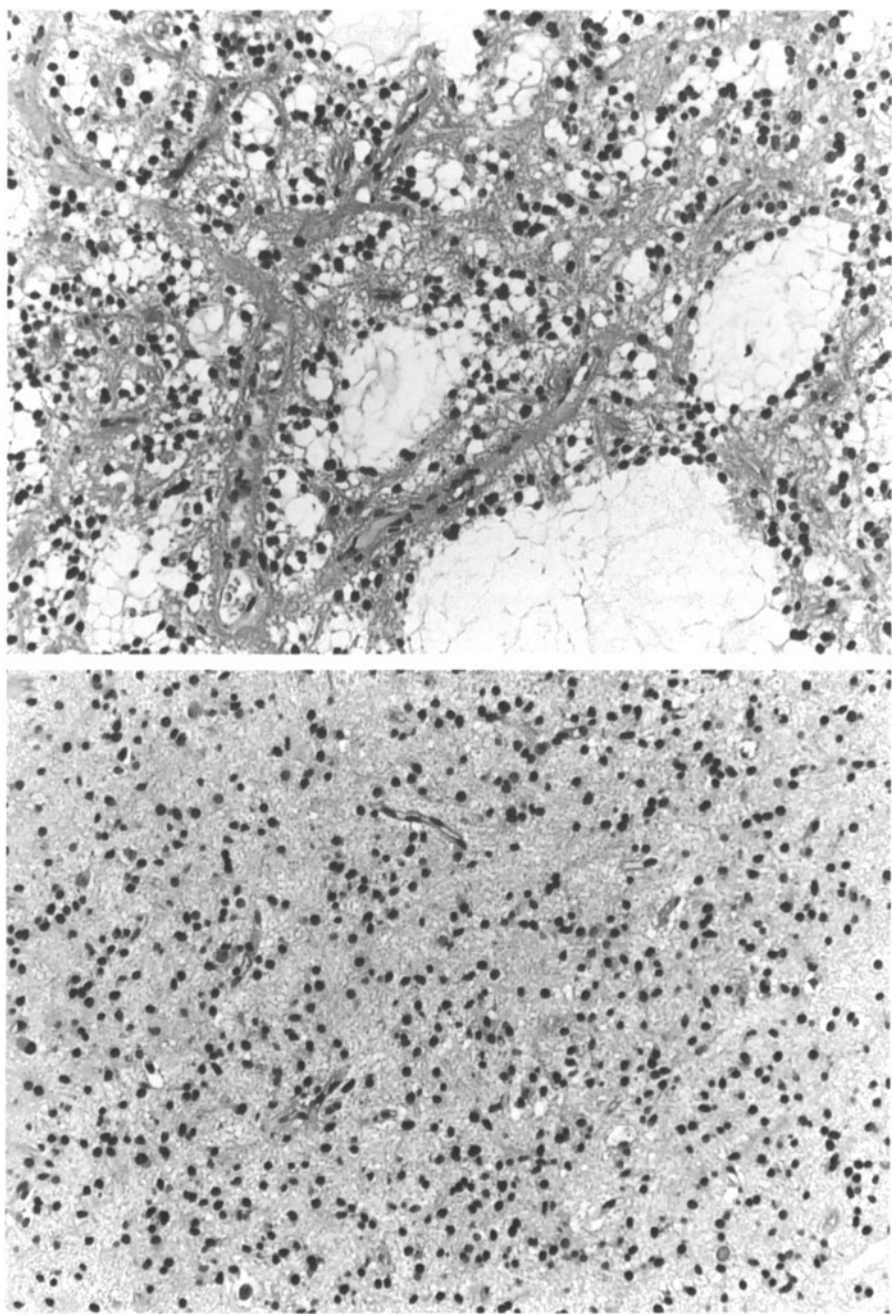
The tumor, initially found in epileptic patients who had undergone surgery, is no longer limited to these conditions. The whole problem has been reviewed by Dumas-Duport [653], according to whom there is a “simple form” and a “complex form” of DNT with a common specific feature, “the glioneuronal element,” which is present in every case.

The glioneuronal element is composed of columns that are perpendicular to the cortical surface, lined by oligodendrocytes and separated by eosinophilic fluid, in which neurons and thin capillaries can be found. These elements occur in foci replacing the cortex. The columns are made up of bundles of axons.

*Simple Form.* The tumors are located in the temporal, frontal, and parieto-occipital lobes and give them an “hypertrophied” appearance. Histologically, they are composed of glioneuronal elements. Clinically, drug-resistant epilepsy is present; neuroradiologically, the lesions appear as circumscribed hypodensities with CT and as hypointensities on T1- and hyperintensities on T2-weighted images with MRI.

*Complex Form.* In addition to glioneuronal elements, the tumor contains glial nodules and dysplasias (Fig. 13.6). Glial nodules may be made of oligodendrocytes, with a fried-egg appearance, or of pilocytic astrocytes, resembling those of “juvenile” or “adult” pilocytic astrocytoma, or even of fibrillary astrocytes or with an anaplastic aspect. Oligoastrocytic nodules occur as well. Necroses, mitoses, and endothelial hyperplasia can be present. Associated cortical lamination changes may occur. LI with proliferating cell nuclear antigen (PCNA) or MIB-1 is very low or absent [2744, 3396].

An immunohistochemical and ultrastructural study carried out on 14 patients confirmed the glioneuronal nature of these lesions. They have a heterogeneous cell



**Fig. 13.6a,b.** Dysembryoplastic neuroepithelial tumor. **a** Microcystic muroid aspect (glioneuronal unit). **b** Oligodendroglial hyperplasia with scattered astrocytes. H&E,  $\times 400$

composition, with many cells resembling oligodendrocytes and a few showing astrocytic and neuronal differentiation. The occurrence of mature neurons is a feature useful for diagnosis [1336].

The tumors are located mainly in the temporal lobe [1736, 2744] with prevailing or extensive involvement of mesial structures [2744, 3396] and less frequently in the frontal and parietal lobes. On CT, they appear hypodense and may show contrast enhancement. On MRI, they appear hypointense on T1- and hyperintense on T2-weighted images with enhancement after gadolinium. The tumors are frequently accompanied by deformities of the overlying cranium.

The diagnosis of DNT is not easy in histological sections. Differential diagnosis must be made with gliomas, mainly gangliogliomas, oligodendrogliomas, and neurocytomas. The main guide in this context is the observation that neurons are never atypical in DNT.

The origin of DNT is thought to be the external granular layer of the cortex [653], because this would explain both the location of the tumors and their histology. The prognosis is very good, even after subtotal surgical removal.

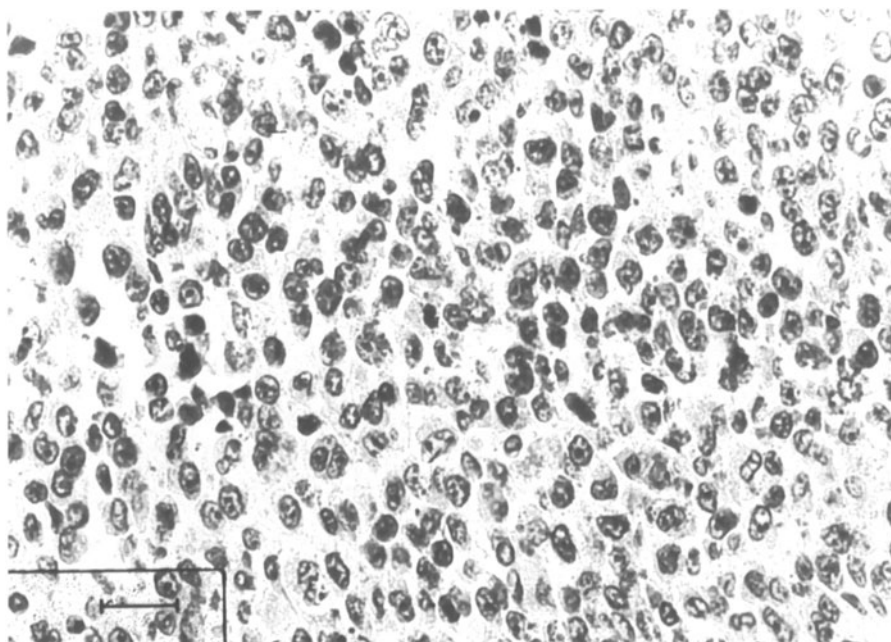
The lesions are now considered to be genuine neoplasms [656, 653, 1688], in contrast to previous evaluations as hamartomas [454, 2680].

### 13.6 Olfactory Neuroblastoma

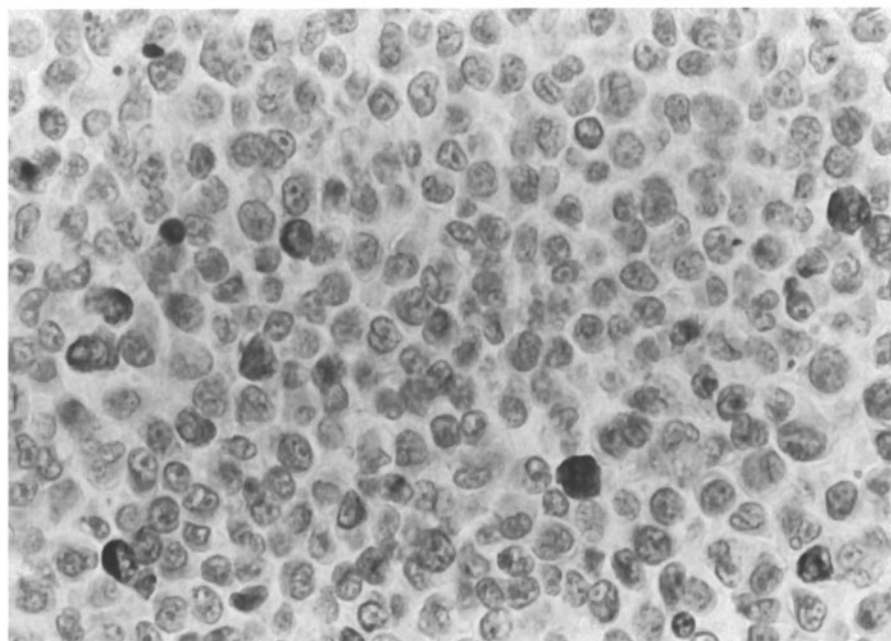
An uncommon tumor that arises high in the nasal cavity is called olfactory neuroblastoma. Its origin has been debated and has been variously attributed to the olfactory placode, sympathetic fibers of the nasal cavity, the sphenopalatine ganglion, and the organ of Jacobson; evidence points to the neurosensory receptor cells in the nasal mucosa [1230] on the basilar cells, which can be precursors of several cell types [3070].

Tumors usually occupy the upper nasal cavity and paranasal sinuses; in localized lesions, the most common presentation is unilateral nasal obstruction and epistaxis, followed less frequently by lacrimation, rhinorrhea, and anosmia. Occasionally, the tumor grows through the cribriform plate and the patient presents with an intracranial mass. In contrast to neuroblastoma, which is a typical pediatric tumor, olfactory neuroblastoma arises in adult age.

The microscopic features of this rare tumor are not homogenous (Fig. 13.7). Some tumors have an epithelial appearance and form tubules and neuroepithelial canals and are called esthesio-neuroepithelioma [3372]. Other cases have the classical aspect of neuroblastoma, with Homer–Wright rosettes or columns of cells in a fine fibrillary matrix; when large true rosettes or canals are present, the tumors are called olfactory neuroblastoma with olfactory differentiation [3191] and do not differ from esthesio-neuroepithelioma. In some cases, lobules of tumor cells in a connective tissue stroma and content of neurosecretory granules in tumor cells suggest a similarity with neuroendocrine carcinoma [3191, 2509]. Most cases show features intermediate between those of neuroblastoma and paraganglioma and are considered to be part of a continuous morphologic spectrum [2509], with the paraganglioma-like portion of the spectrum accounting for the majority [1337]. No significant difference is found



a



b

**Fig. 13.7a,b.** Olfactory neuroblastoma. **a** Nuclei with prominent nucleoli. H&E,  $\times 400$ . **b** Neuroblastic tumor with scattered neurofilament (NF)-positive cells, SMI 31-32. PAP-DAB.  $\times 400$

between the variants with regard to their ultrastructural features. The neuroectodermal nature is confirmed by the finding of neurosecretory-type, dense core granules and of processes containing microtubules.

Immunohistochemistry is very helpful in assessing the diagnosis; immunoreactivity for neuronal or neuroendocrine markers is a necessary requisite to rule out carcinoma and lymphoma and, rarely, a pituitary adenoma in the nasopharynx or meningioma of the anterior cranial fossa.

Synaptophysin and chromogranin A are expressed more frequently by paraganglioma-like tumors, whereas neurofilament proteins are expressed more commonly by neuroblastic tumors. In rare cases, features suggesting a ganglionic differentiation are found. S-100 protein-positive cells are frequently found at the periphery of tumor lobules, analogous to the subtentacular cells of paraganglioma, whereas they are absent in neuroblastoma-like tumors.

Olfactory neuroblastoma is radiosensitive, and localized lesions have a good prognosis: 100% survivors at 5 and 10 years [1337]. The occurrence of metastases to cervical lymph nodes, lung, and bones at either presentation or recurrence carries a worse prognosis. Higher incidence of S-100-positive cells and MIB-1 lower than 10% LI have been found to be statistically significant variables for improved survival.

## Pineal Gland Tumors

### 14.1

#### The Pineal Gland

The pineal gland is attached to the posterior roof of the third ventricle between the posterior and the habenular commissures, and between the pineal and suprapineal recesses. It develops at the beginning of the second month of gestation as an evagination of the diencephalic roof. Concerning function, it is active in the transmission of information regarding the length of daylight, the regulation of reproduction in mammals, and the circadian rhythms. In fish and amphibians, the parenchymal cells (the pineocytes) have a photoreceptor function, transforming light into electrical signals.

In birds, the gland is a photoendocrine transducer transforming light into hormonal signals. In mammals, it behaves as a neuroendocrine transducer, transforming electrical into hormonal signals [115].

The main product of the pineal gland is melatonin, or *N*-acetyl-5-methoxytryptamine. Its synthesis depends on lighting conditions and is stimulated by  $\beta$ -adrenergic sympathetic postganglionic fibers, which in turn are stimulated by darkness. Light has an inhibitory function. Norepinephrine and serotonin are released at the sympathetic endings. The metabolic path begins from plasma derived tryptophane and arrives at melatonin. The stimulation of the  $\beta$ -adrenergic receptors activates adenylcyclase so that the cyclic adenosine monophosphate (cAMP) and *N*-acetyltransferase levels increase.

The photic stimulus reaches the gland via a complex pathway which begins with the retino-hypothalamic tract and then passes to the suprachiasmatic nucleus, but stimuli may also arrive directly from the geniculate body [2302]. The most efficacious wavelength is yellow-green [3726]. Through the lateral hypothalamus and the medial prosencephalic bundle, the stimuli descend in the intermediolateral column of the spinal cord and from here via the preganglionic fibers reach the superior cervical ganglia [439]. The postganglionic fibers reach the gland through the “*nervi conarii*” which pass through the tentorium.

Histologically, the gland, which is present in all vertebrates apart from alligators and armadillos, has a capsule and is composed of lobules separated by connective tissue septa. It contains parenchymal elements, the “pineocytes,” and interstitial cells. The former show features of paraneurons [3483] and of elements of the amine precursor uptake and decarboxylation (APUD) system [2592], being positive for neuron-specific enolase (NSE) and containing secretory granules. They do not have axons but argyrophilic processes which are directed towards the blood vessels, on

which they end with club shaped expansions [700]. Ultrastructurally, pineocytes contain 20- to 25-nm microtubules, especially in the processes, endoplasmic reticulum (ER), multivesicular bodies (MVB), and mitochondria. Distinguishing features are vesicle-crowned rodlets (VCR) or "synaptic ribbons," fibrous filaments and paired twisted filaments (PTF) arranged parallelly. VCR consist of a central osmiophilic area, surrounded by 60-nm clear vesicles [1557].

In the neonatal rat, some features of photoreceptor cells may be found [3785], and this is consistent with the glandular expression of the retinal S antigen [752, 1752]. This is a 48-kDa protein which binds to rhodopsin. It has been found in human fetal and adult pineocytes [2615]. The interstitial cells are glial fibrillary acidic protein (GFAP)-positive astrocytes [1426].

The production of melatonin is regulated by light, and the pineal gland transduces periodic photic stimuli intervening in the temporal organization of various metabolic, physiological, and behavioral processes. It has endocrine and nonendocrine functions [844]. Effects on reproduction and on the thyroid and adrenal glands belong to the former [2760, 2761]. It has no antigonadotropic effects [2760] but influences, via the hypothalamus, prolactin, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) production. It may also act directly on the pituitary [2762]. The nonendocrine functions are those affecting locomotion, aggressiveness, analgesia, response to stress, electrical cortical activity and sleep mechanism. They are involved in sleep disturbance, pathogenesis of epileptic fits, hibernation, and thermoregulation [844]. Melatonin acts mainly via the hypothalamus, and it seems that its action is exerted on microtubules [3700]. It also has an influence on the growth of tumors in general, playing an inhibitory role by its action on mitotic activity and immunocompetence [2762].

Tumors of the pineal gland have to be separated from those of the pineal region, the latter being composed mainly of astrocytomas and germ cell tumors. The true tumors of the pineal gland are rare and represented by pineocytomas and pinealoblastomas, which vary in their degree of differentiation and arise from pineocytes; astrocytomas arise from interstitial astrocytes. Pineocytomas and pinealoblastomas are formed by mature (pinealocytomas) or immature (pinealoblastoma) elements; however, transitional forms between the two exist, so the above-mentioned forms represent the two poles of a spectrum. Their true incidence is not easy to calculate, but it is low: 0.4% according to Zülch [3799]. In other series it is 1% in adults and 8% in infants [1367]. Pinealoblastomas have a peak incidence in the first decade of life, and pineocytomas in the third [1311].

## 14.2

### Pineal Gland Tumors

In addition to pineocytomas, tumors with intermediate differentiation, mixed tumors with elements of both pineocytomas and pinealoblastomas, and pinealoblastomas must be considered.

The clinical symptomatology is variable. There may be increased intracranial pressure from hydrocephalus, due to the obstruction of the third ventricle or of the aqueduct. Focal symptoms are represented mainly by Parinaud's syndrome

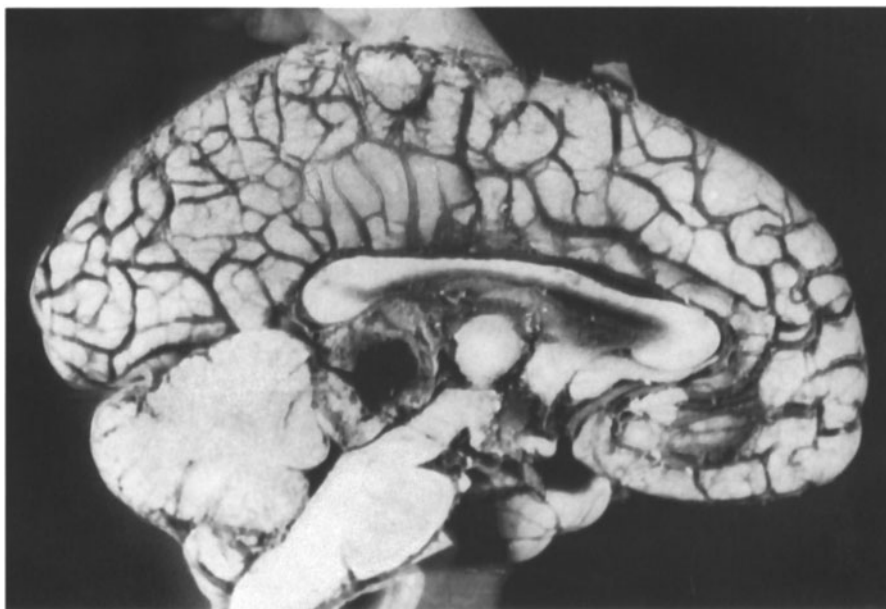


Fig. 14.1. Pineocytoma

with gaze paralysis. Endocrine dysfunctions are rare and are due to involvement of hypothalamus. Apoplexy from an intratumoral hemorrhage is possible.

As far as imaging is concerned, magnetic resonance imaging (MRI) is the procedure of choice. It demonstrates the tumor and its relation with the surrounding structures. Necroses and hemorrhages are more frequent in pinealoblastoma. Calcifications may be found, as well as cysts in pineocytomas.

### 14.2.1

#### Pineocytoma

##### 14.2.1.1

##### *Macroscopic Appearance*

The tumor is situated at the site of the pineal gland, is well circumscribed, pushes towards the third ventricle, and displaces the aqueduct (Fig. 14.1). The pineal gland may be completely destroyed or enlarged. The cut surface is grayish-pink, granular, gelatinous, and cystic or necrotic-hemorrhagic (Fig. 14.2).

##### 14.2.1.2

##### *Microscopic Appearance*

The description of the microscopic appearance is drawn from major series of 28 cases [1311], 13 cases [311], and 20 cases [1557]. The tumor cells resemble those of



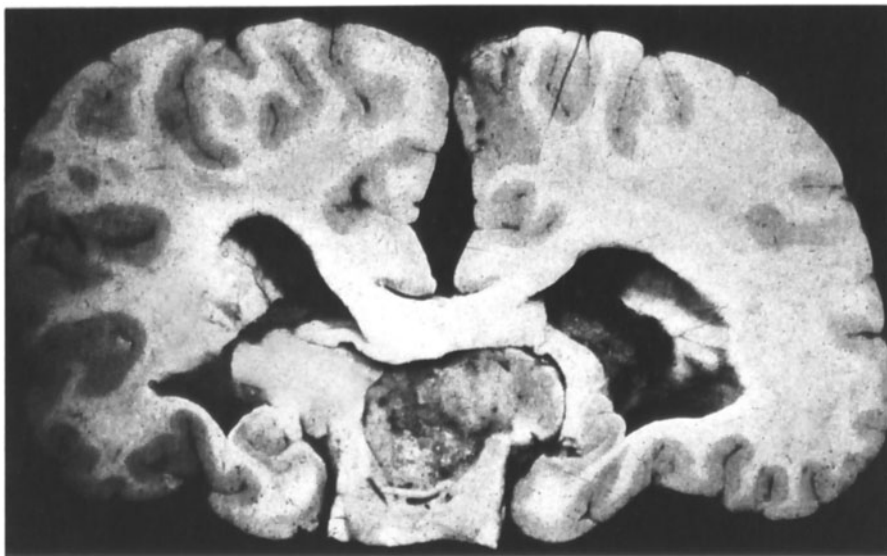


Fig. 14.2. Pineocytoma

the normal pineal gland. They show a medium density and are arranged in lobules, separated by a delicate stroma and small blood vessels. The cytoplasm may be moderate in amount, with a polar aspect as cells are generally arranged around blood vessels to which they send out delicate processes (Fig. 14.3). Mitoses are not invariably present but may be found in variable numbers. Homer–Wright rosettes may be present, and with silver impregnation delicate club shaped processes may be identified.

According to some, the pineocytoma rosettes can be distinguished from the Homer–Wright rosettes of neuroblastomas by their larger and irregular central part and a tendency to become confluent (Fig. 14.4) [311]. Large formations are called pineocytomatous rosettes [308]. Upon silver impregnation, tangles of argentophilic processes may be found in the center of the rosettes.

Neuronal, astrocytic, or neuronal and astrocytic differentiations have been described [1311]. Neuronal differentiation may be indicated either by the presence of rosettes or by the presence of neoplastic ganglion cells with atypical processes, Nissl's granules, and so on. The astrocytic differentiation is confirmed by phosphotungstic acid hematoxylin (PTAH) staining or by the demonstration of GFAP. Electron microscopy confirms the existence of neuronal characteristics demonstrating, apart from the endoplasmic reticulum, ribosomes and dense core vesicles (Fig. 14.5), and in particular microtubules and membranous whorls (Fig. 14.6) [1259]. The features, however, are so nonspecific that they may be thought to represent an undifferentiated primitive tumor with some tendencies to differentiate [2114]. Therefore, gangliogliomatous [2883, 2427] or astrocytomatous [2798, 700, 308] pineocytomas have been described, even with malignant characteristics [1311].

It should be noted that some features, such as the presence of dense-core vesicles, cilia with a 9+0 complex axial filament, synaptic bands, bulb endings of microtubule

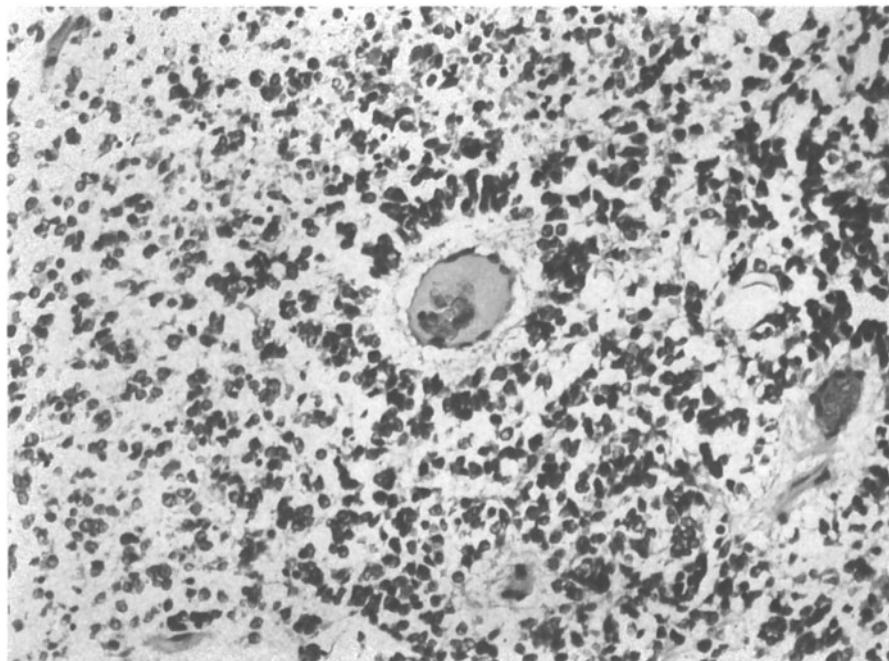


Fig. 14.3. Pineocytoma, cells arranged around a vessel. H&E,  $\times 400$

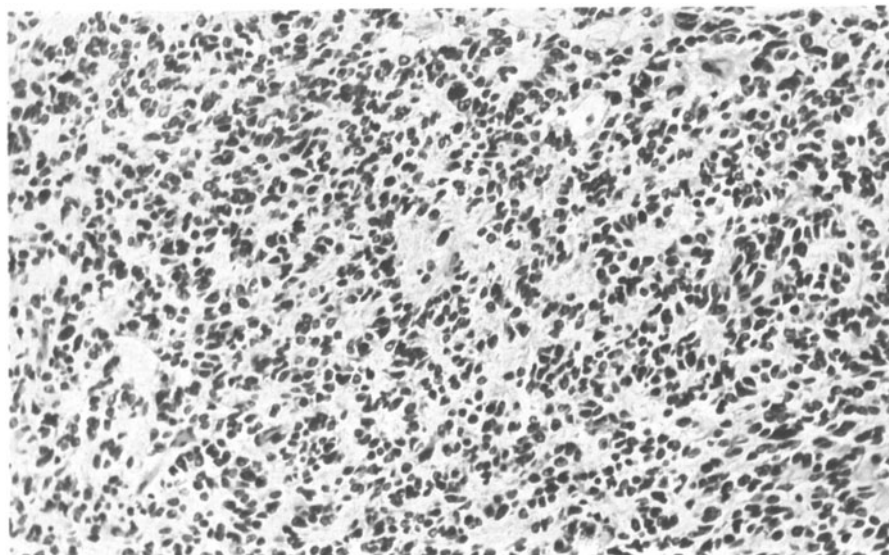


Fig. 14.4. Pineocytoma, rosettes. H&E,  $\times 200$

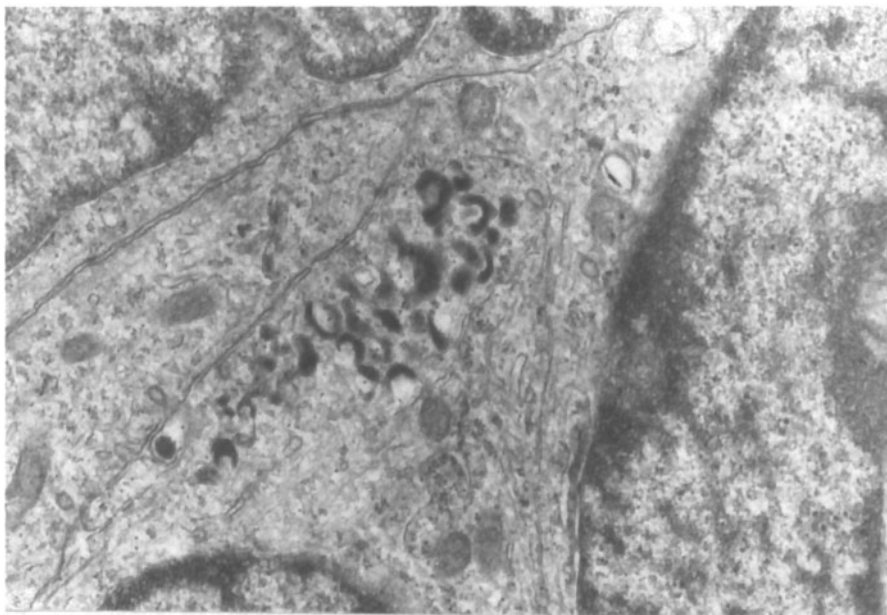


Fig. 14.5. Pineocytoma, dense core vesicles. Uranyl acetate, lead citrate stain,  $\times 20\,000$

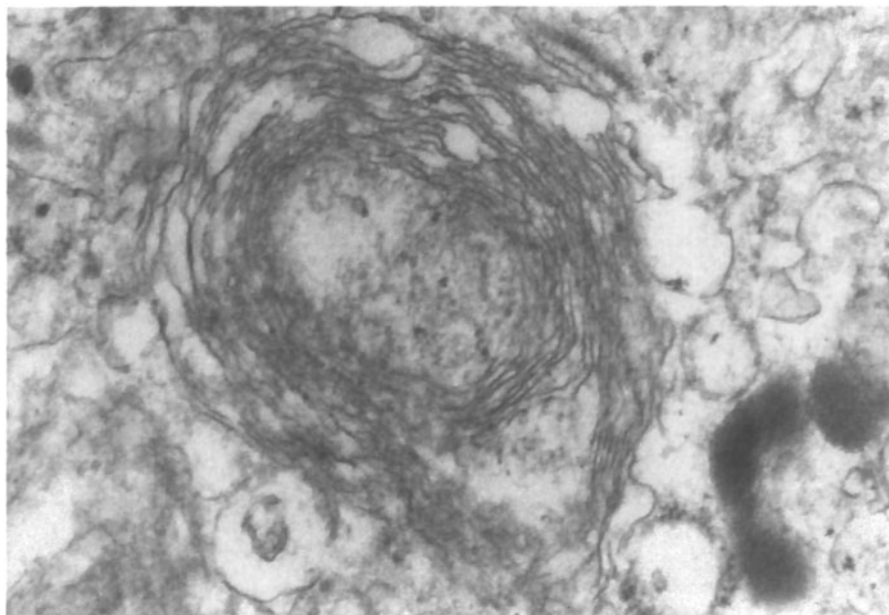


Fig. 14.6. Pineocytoma, membranous whorls. Uranyl acetate, lead citrate stain,  $\times 40\,000$

fascicles, and light-core vesicles, are similar to those found in an experimental pineocytoma induced in hamsters by human JC papovavirus [3523]. In this tumor, the oncogenesis seems to have simulated the ontogenesis of the gland and have reproduced rudimentary photoreceptor elements.

Pineocytomas must be differentiated from the rare pineal cysts, and this is not an easy task, particularly when small specimens are submitted. Lobules of parenchymal cells are associated with an intense gliosis in the cysts, which are to be considered as nontumoral entities [1705, 2173].

### 14.2.1.3

#### *Treatment and Prognosis*

The treatment of pineal gland tumors comprises surgery, with total or partial resection, or biopsy and radiotherapy.

The prognosis of pineocytomas is not easy to establish, because there are so few in the various series [2524, 803] and because of their difficult delimitation from pinealoblastoma. Furthermore, it is not easy to codify their response to radio- and chemotherapy.

On the basis of experience at the Mayo Clinic, doses of 50–55 Gy to the area of gross tumor and craniospinal irradiation in patients with seeding potential are recommended [3041].

Generally, the prognosis is poor and survival does not extend beyond a few years if there is no differentiation, as in pinealoblastomas. If there is differentiation, survival may be prolonged for some years [1311]. Metastasis via the cerebrospinal fluid (CSF), which is easily recognisable, is less probable than in pinealoblastoma. In the experience of the Philadelphia group, infantile pineocytomas tend to be more aggressive than those of adults, the incidence of leptomeningeal seeding is high, and recurrences generally arise within a short time. They advocate, therefore, craniospinal irradiation [632]. However, in the experience of the San Francisco group, leptomeningeal spread is less frequent (one in five), as is local recurrence after surgery and radiotherapy. They advocate craniospinal irradiation only in the presence of documented dissemination [738].

### 14.2.2

#### **Pinealoblastoma**

#### 14.2.2.1

##### *Macroscopic Appearance*

Pinealoblastoma has ill-defined margins, infiltrates the surrounding tissue and abuts on the third ventricle, and the gland appears to be destroyed (Figs. 14.7, 14.8). It has a grayish-pink appearance, is gelatinous, and is sometimes necrotic and hemorrhagic.

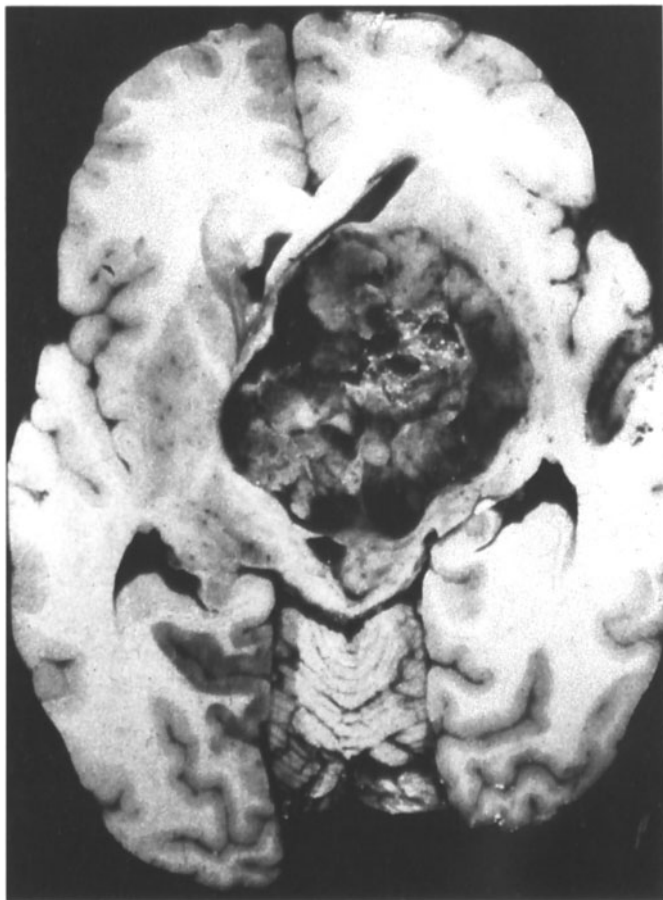


Fig. 14.7. Pinealoblastoma

#### 14.2.2.2

##### *Microscopic Appearance*

Histologically, pinealoblastomas have a high cell density and are composed of cells with small, dark nuclei, closely resembling medulloblastoma. Mitoses are frequent, but they may also be absent. The cells may sometimes demonstrate a single, short process with silver impregnation, but they do not have a particular arrangement and form only ill-defined Homer-Wright rosettes (Fig. 14.9). According to some, a mosaic effect has sometimes been found, with the formation of lobules in which there are transitional elements in the developmental sense [2904].

Pineocytomatous features may coexist, or transitions between the two tumor appearances may be found. Retinoblastic differentiation can also be present, with the formation of “fleurettes” [3468] and of Flexner-Wintersteiner rosettes, typical of retinoblastoma (Fig. 14.10). The fleurettes represent an attempt at differentiation toward

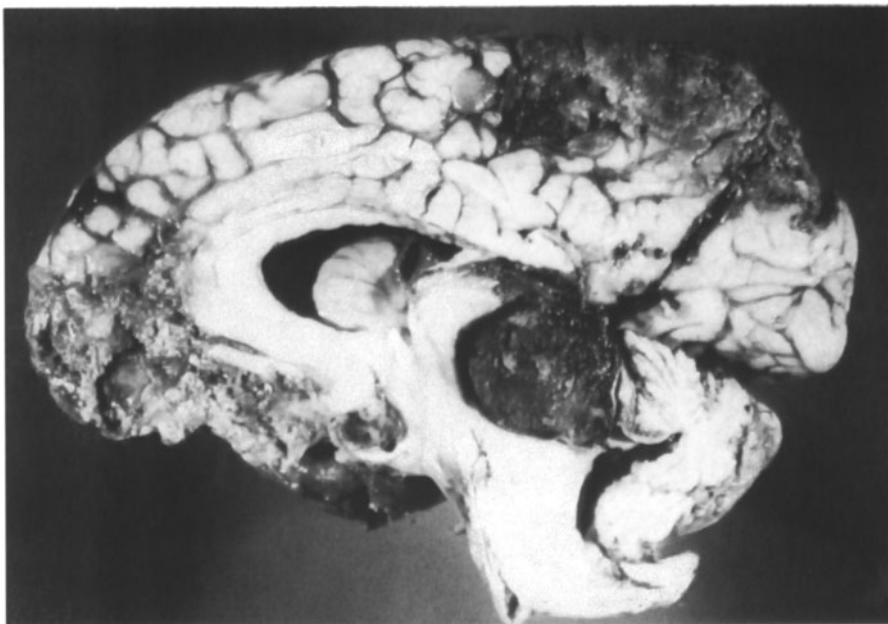


Fig. 14.8. Pinealoblastoma

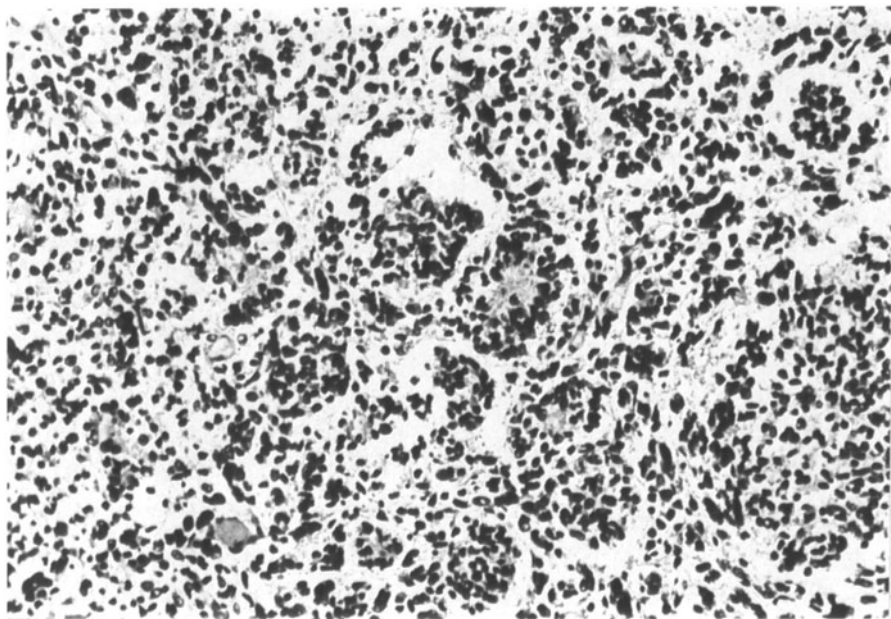


Fig. 14.9. Pinealoblastoma, high cell density and ill-defined Homer-Wright rosettes. H&E,  $\times 300$

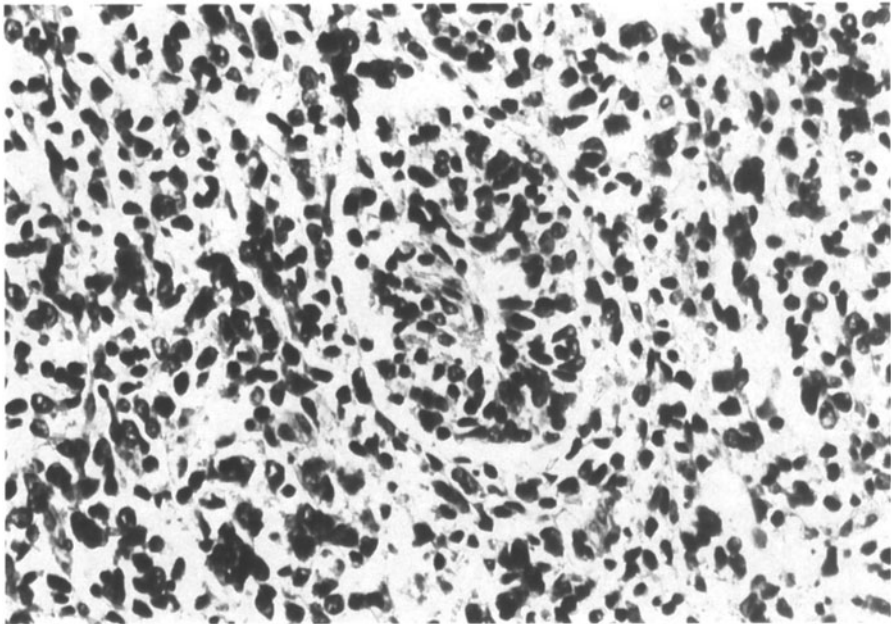


Fig. 14.10. Pinealoblastoma, architecture resembling fleurettes. H&E,  $\times 400$

photoreceptors [1311, 3291, 311]. Immunoreactivity for S retinal antigen, characteristic of retinoblastoma [752], has also been demonstrated in cells of the pineal parenchyma as well as in pineocytomas and pinealoblastomas [2615, 614].

Neuronal differentiation has also been described in some cases [1311, 3244, 2815, 2487], and in one case retinoblastic differentiation and ganglionic and glial elements were seen [3244]. It is not yet clear whether the astrocytic elements are derived from the astrocytes of the pineal gland or represent multipotential differentiation of pineocytes, although the second hypothesis seems more probable [2904]. The same concept can be applied to cells with neuronal features, which might derive from normal neurons of the gland and not be a product of differentiation [1255].

Melanotic deposits have been described [226, 1311, 3051], which correspond to normal findings in the gland during development. In a case, rhabdomyoblastic features were also described, together with neuroblastic, ependymoblastic, and retinoblastic elements, which can be explained by the close topographic relationships between the neural crest and the neural tube at the level of the prosencephalon [3051]. Necrosis, hemorrhage, and calcification in the tumor may be found, but there is never endothelial hyperplasia.

Electron microscopic examination has been carried out in only a few cases. In one, analogies with photoreceptor elements of the pineal gland of inferior vertebrates were found [1717].

In the tumors of the human pineal gland, neither melatonin nor the enzyme which synthesizes it (hydroxyindol-*O*-methyltransferase) have been immunohistochemically found.

#### 14.2.2.3

##### *Prognosis*

Metastasis via the CSF into the ventricles and subarachnoid spaces is common in pinealoblastoma [1740, 2524], and the prognosis is dismal [1367], although long-term survivors have been reported [3485]. Because of the paucity of cases, it has not been possible to glean precise clinical statistics from surveys. Similarly, it is difficult to evaluate the efficacy of treatment procedures such as radio- and chemotherapy [632] (see also Sect. 14.2.1.3 on pineocytomas).

#### 14.2.4

##### **Trilateral Retinoblastoma**

Cases featuring an association between bilateral retinoblastoma and pinealoblastoma have been described in children. This condition goes under the name of “trilateral retinoblastoma” [121], and it is hereditary, while solitary pinealoblastoma is only exceptionally familial [1923]. Retinoblastoma may unusually be unilateral in this syndrome. Up to date, 30 cases have been reported [2904]. The association has a special significance in the context of pineal tumors, demonstrating the photoreceptor origin of the cells which undergo neoplastic transformation.

In very rare cases, a variant of the trilateral retinoblastoma, a retinoblastoma-like tumor in the supra- or parasellar region, has been described [121, 1683]. In one [3096], it was undifferentiated and exhibited immunohistochemical positivity for the S retinal antigen.

### 14.3

#### **Pineal Cysts**

Small, asymptomatic cysts of the pineal gland are commonly discovered in adults by CT or MRI and at autopsy. They originate from the enlargement of the pineal cavity during development, from defective vascularization of a glial plaque, or from degeneration of pineocytes [1590]. Large, symptomatic cysts, in contrast, are rare; few cases have been reported in recent years [1705, 2173, 2473]. They derive either from hemorrhages or from enlargement of preexisting cysts by hormonal influence [1705].

Clinically, they show increased intracranial pressure, obstructive hydrocephalus, and Parinaud’s syndrome with neurological signs of brain stem involvement. They are easily visualized by CT; by MRI they appear as homogeneous masses on T1-weighted images and are more intense than CSF on T2-weighted images. Histologically, the wall of the cyst is composed by an external fibrous layer, a middle layer of pineal parenchyma with calcification, and an inner layer of glial tissue with Rosenthal’s fibers. From the histological point of view, the main problem is the differential diagnosis from pineocytoma and pilocytic astrocytoma [861], especially when the cyst wall has not been properly embedded in paraffin. The absence of a layered architecture and of a hypocellular population of astrocytes in contact with



the pineal parenchyma and the occurrence of microcysts are indicative of pilocytic astrocytoma. Pineocytoma is more easily recognizable, unless it resembles normal pineal gland. The observation of silver-positive processes, rosettes, and mitoses may be of help, and proliferation markers may also be useful. Surgical treatment can be curative

## Embryonal Tumors

### 15.1

#### Medulloepithelioma

Medulloepithelioma is an extremely rare tumor which, according to Bailey and Cushing [133], is a primitive and multipotential tumor par excellence. It was fully described later [3455], and up to now almost 30 cases have been reported. The tumor recounts the architecture of the primitive medullary epithelium and its capacity to differentiate. In a personal collection, there is one such case.

It is a tumor of infancy, usually located in the hemispheres, but it has also been described in the posterior fossa [225, 2957, 301] and in the cauda equina [1593].

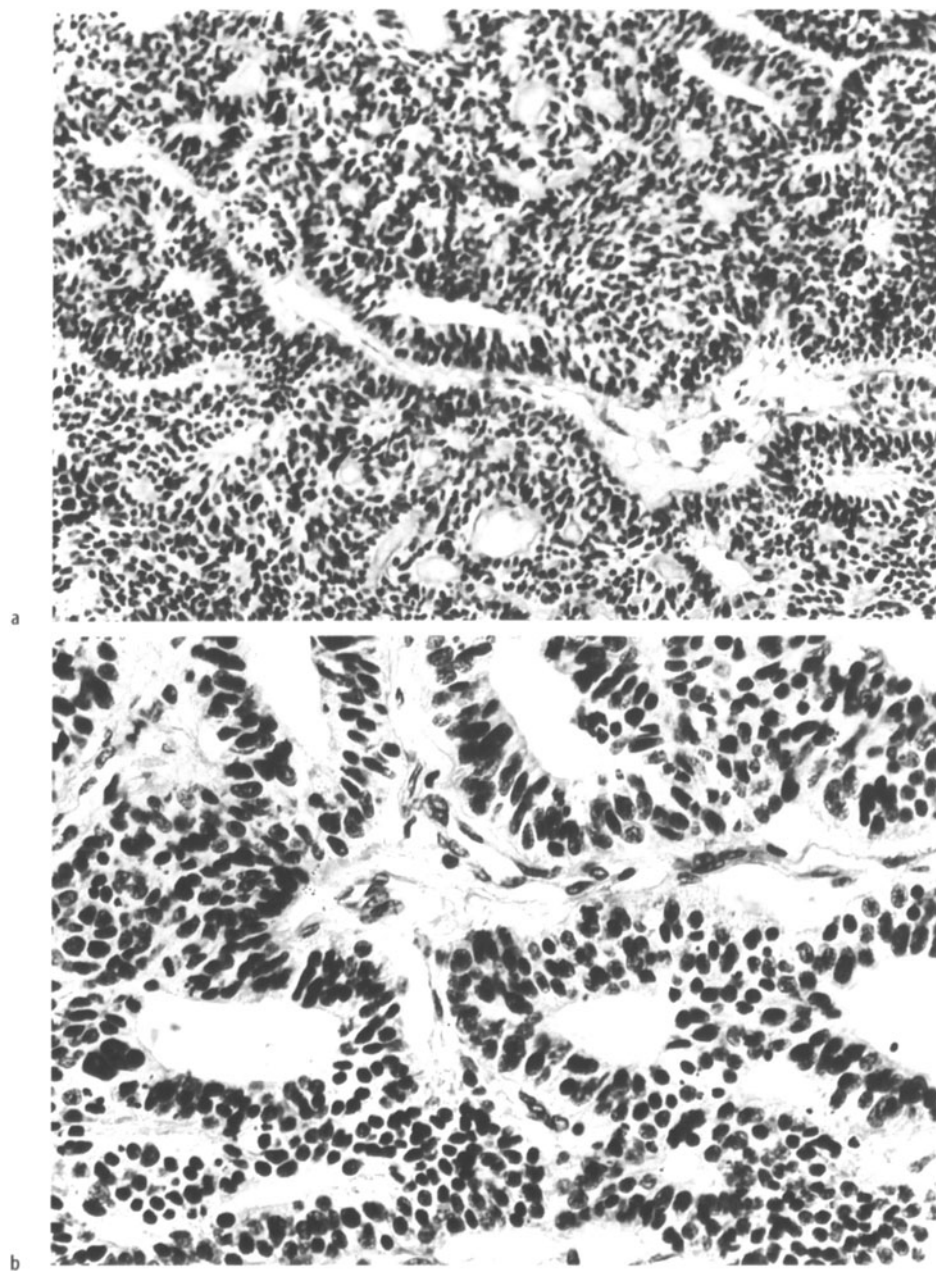
Macroscopically, it appears as a circumscribed, grayish, hemorrhagic, necrotic or cystic tumor.

Histologically, it features papillae and tubules formed by columnar or cuboidal cells which simulate the neural tube (Fig. 15.1). There is a periodic acid-Schiff (PAS)-positive limiting membrane, of doubtful nature, on the luminal surface and an external limiting membrane, which is strongly PAS-positive and rests on a delicate connective tissue. Mitoses are frequent and found close to the lumina of the tubules.

The tumor is capable of differentiating toward neuroblastic, ependymal, astrocytic, or oligodendrocytic lines and sometimes in all directions [2978, 301].

Four cases have been the object of an accurate immunohistochemical study with a panel of antibodies and antisera [410]. It has been observed that, apart from the medullary primitive epithelium, there are neuroblastic, ganglion, astrocytic, ependymoblastic and ependymal areas; in one case, even an area of polar spongioblastoma was found. The primitive medullary cells were found to stain positively for GFAP, vimentin, and class III  $\beta$ -tubulin. It is important to note that vimentin marking was positive in ependymoblastic areas and in ependymal rosettes. The stroma is of variable consistency and contains blood vessels. It is susceptible to metaplasia, as in one case in which there was formation of cartilage, bone, and striated muscle [105], to the point of suggesting a mixed mesenchymal and neuroepithelial origin.

The differential diagnosis has to include ependymoma, malignant plexus-papilloma, and teratoma. The diagnosis is difficult when differentiation signs are poor or lacking. The biological behavior is that of a malignant tumor with spread to the subarachnoid spaces [2659], and extraneural metastases [3511] have also been reported.



**Fig. 15.1a,b.** Medulloepithelioma. **a** General architecture with tubules and rosettes. H&E,  $\times 200$ . **b** Columnar and cuboidal cells of tubules, many mitoses. H&E,  $\times 400$

## 15.2 Medulloblastoma

Medulloblastoma was separated off as a distinct tumor entity by Bailey and Cushing and given the name of “spongioblastoma cerebelli,” which was later modified by the same authors [132] into “medulloblastoma cerebelli,” to avoid confusion with other known tumors with the same label. It was later variously defined, for example as a neurospongioma [2862], an isomorphous glioblastoma [1393], or a granuloblastoma [3311], reflecting the various opinions on its origin. The tumor is generally considered to be formed by immature and undifferentiated elements, which are capable of differentiating toward glial and/or neuroblastic lines.

A decline in incidence of medulloblastoma in children since 1985 in Avon, United Kingdom, has been shown; it might have been caused by the introduction of periconceptional multivitamin supplementation in the 1985 [3433]. On this basis, a causal similarity between primitive neuroectodermal tumors (PNET), including medulloblastoma, and neural tube defects is conceivable [385].

### 15.2.1 Frequency, Age and Clinical Features

Medulloblastoma is a fairly frequent tumor, representing about 4.2% of all CNS tumors [3803]. In infancy, it is much more common, with values of around 20%–25%. In the posterior fossa, it is almost as frequent as cerebellar astrocytoma. There is a slight prevalence in men [2797, 3799, 2994]. The incidence peak is found between 7 and 12 [3803] or 5 and 10 years [2994]. Medulloblastomas are rarely found over the age of 50 years [97, 511]. Patients with laterally located medulloblastoma are older [2882].

Congenital cases have been described [1167, 188, 57, 1673]. The incidence is 1/200 000 children per year. Environmental factors of etiological importance have been sought but not found. It was noted that the increase in incidence of this tumor in the years 1954–1958 was associated with the use of polio vaccine contaminated with SV40 virus [868].

Familial occurrence of medulloblastoma has been reported [3437]. Apart from posterior fossa clinical syndrome, there is no specific and pathognomonic presenting sign. In children, early symptoms include changes in behavior and irritability or lethargy, followed by headache and vomiting. Intracranial hypertension occurs, due to obstructive hydrocephalus. Paralysis of the sixth cranial nerve may follow together with a midline cerebellar syndrome. A lateral cerebellar syndrome is more frequent in desmoplastic variant.

### 15.2.2 Macroscopic Appearance and Imaging

The tumor usually arises in the vermis and presents as a soft, gray-pink mass, sometimes with evident necrosis. At times, it is so soft that it can be aspirated during surgical intervention. In some cases, especially if the tumor arises in the cerebellar

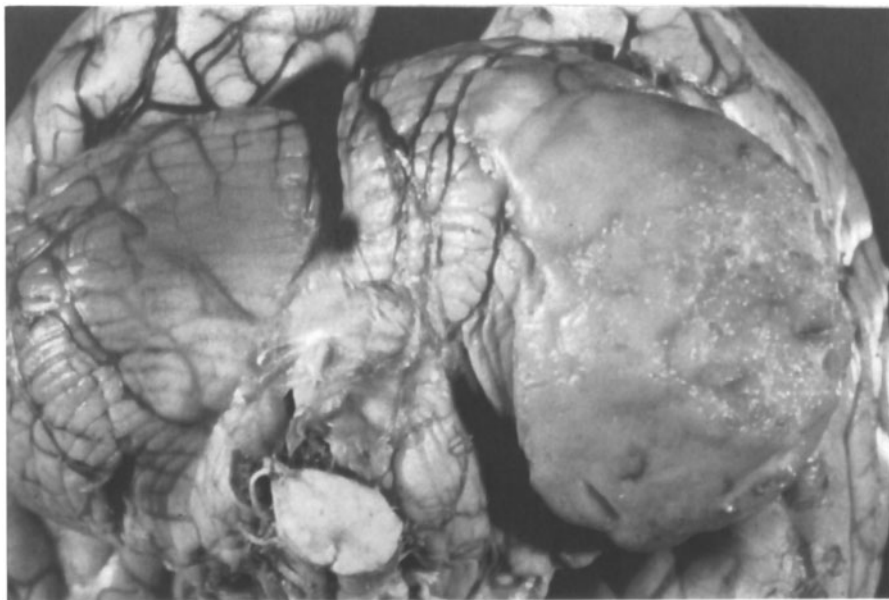


Fig. 15.2. Medulloblastoma of the cerebellar hemisphere



Fig. 15.3. Medulloblastoma of the vermis filling the fourth ventricle

hemispheres, it may be very hard and involve the meninges which appear thickened (Fig. 15.2). Expanding into the cerebellum, the tumor may invade the roof of the fourth ventricle and grow, filling the ventricle (Fig. 15.3). It may grow up to the aqueduct or block the foramina of Magendie and Lushka. Locally, it infiltrates the cerebellar cortex but may fungate into the subarachnoid spaces and then re-enter the cerebellum, including wide portions of the cerebellar lamellae.

On computed tomography (CT) scan, it appears as a hyperdense mass with either uniform or heterogeneous contrast enhancement. Small cysts may be present. The mass is often on the cerebellar vermis and fills the fourth ventricle.

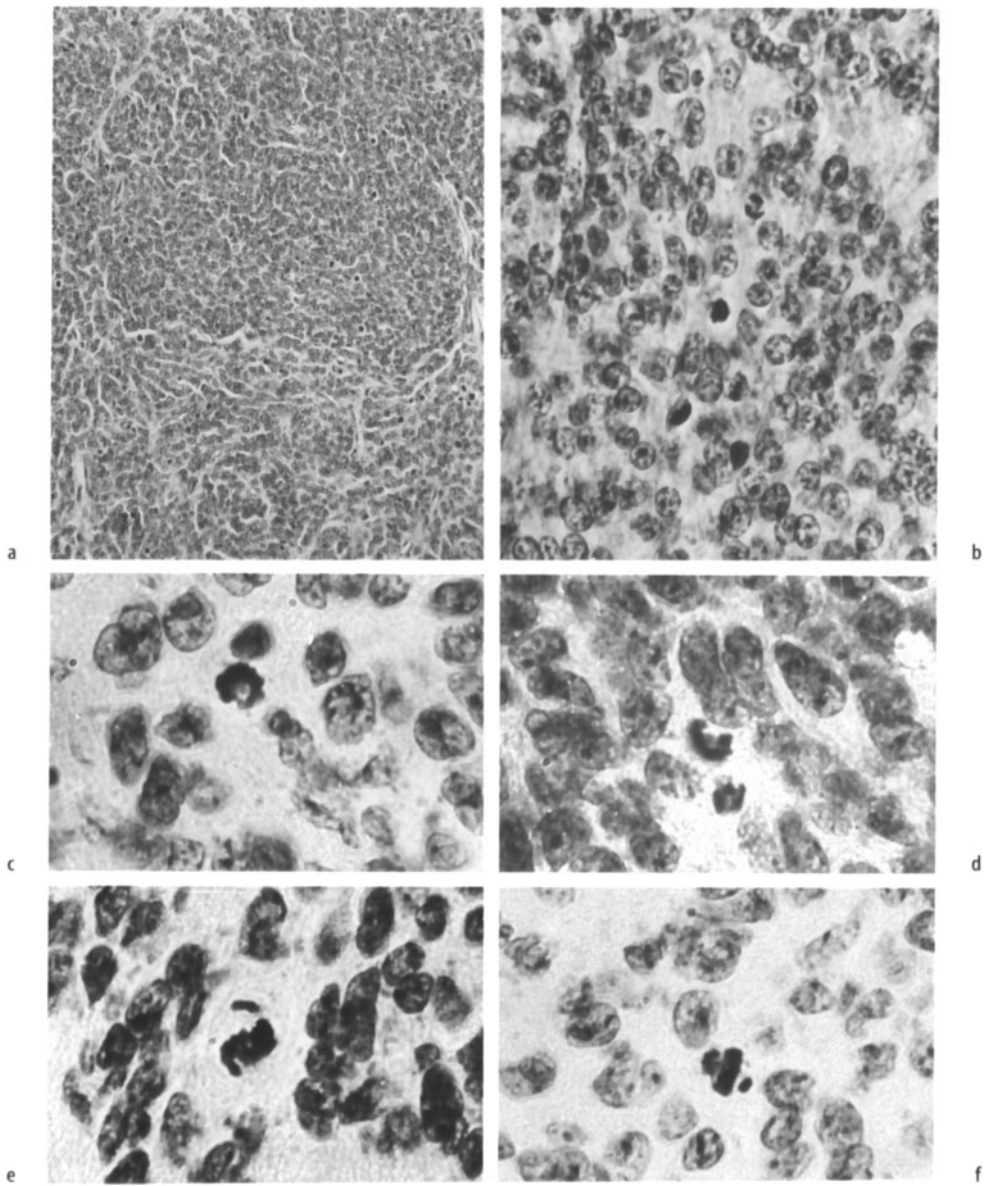
### 15.2.3

#### Microscopic Appearance

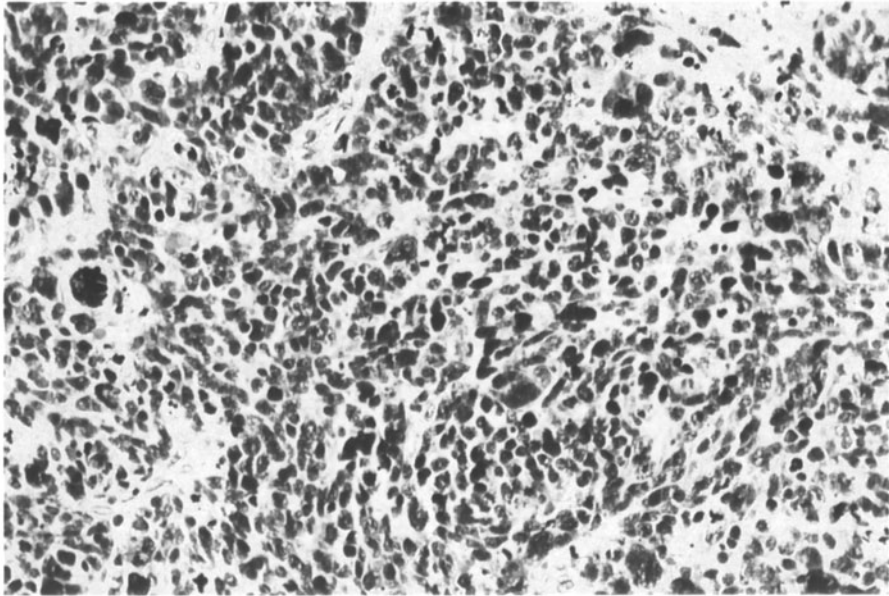
The tumor is characterized by a very high cell density (Fig. 15.4a). The cells are relatively isomorphous or moderately polymorphous with a roundish or elongated shape, a scanty, sometimes pear-shaped cytoplasm, and a small apical process or with a double panache at the sides of the nucleus. The nuclei are hyperchromatic. Mitoses are very frequent (Fig. 15.4b) and very often atypical, more so than appear on superficial examination (Fig. 15.4c–f). The more common pathological findings include “laggard chromosomes” and “three group metaphase” [3005]. Quantitative data demonstrate that 25% of mitoses are abnormal and that 30% of these are bizarre [3090]. The nuclei in general are relatively isomorphous, but occasionally some polymorphism is observed, and sometimes there are true monstrous nuclei [1297, 3480], located particularly along the stromal septa which separate the tumor lobules (Fig. 15.5a).

Cases with cells and nuclei of larger dimensions are not rare. The tumor tends to have a lobular structure, and the lobules are separated by reticulin septa connected with blood vessels (Fig. 15.5b). The cells tend to form pseudorosettes, which are known as Homer–Wright rosettes (Fig. 15.6a). They are composed of cells arranged around a fibrillary center similar to those of neuroblastoma. Necroses appear as small, circumscribed foci which at times exhibit hypercellularity at their border or even pseudo-palisades. Small calcifications may be present. Lymphocyte-like nuclei, which correspond to cell necrosis or to pathologically arrested mitoses, are found throughout the tumor (Fig. 15.6b,c). The DNA of these cells appears to be “denatured” [3005]. The morphology of these nuclei corresponds to that of apoptosis, with nuclear chromatin condensed against the nuclear membrane, split until the formation of apoptotic bodies (Fig. 15.7a,b). These nuclei are positive after ISEL technique, i.e., in situ end labeling with digoxigenin labeled nucleotides and terminal transferase (Fig. 15.7b,c) [3037, 3039a].

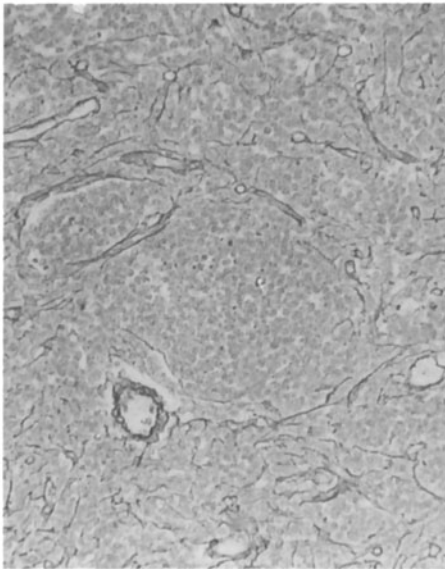
The vascularization of the tumor is scanty when considered in the light of its speed of growth. It consists mostly of blood vessels of small caliber. There are, at times, larger vessels, but thrombosis is usually lacking and endothelial proliferation is moderate. However, at times the stroma is particularly represented: Blood vessels show thickened walls containing proliferating nonendothelial cells or even intraparietal proliferations of tumor cells (Fig. 15.8a).



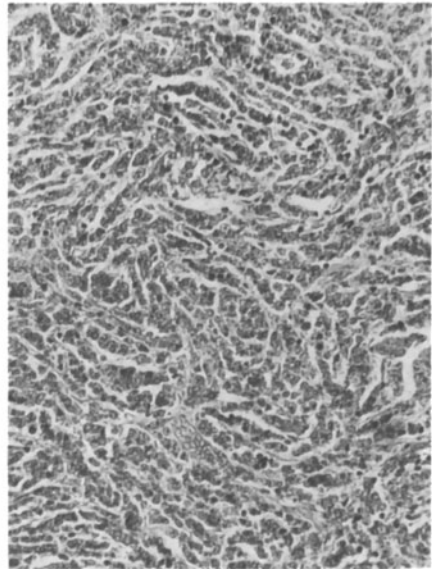
**Fig. 15.4a–f.** Medulloblastoma. **a** Isomorphic cells with high density. H&E, ×200. **b** Frequent mitoses. H&E, ×400. **c,d** C-mitoses. **e** Laggard chromosomes. **f** Three-group metaphase mitosis. Carmalum, ×1000



a



b



c

**Fig. 15.5a–c.** Medulloblastoma. **a** Polymorphous nuclei. H&E,  $\times 400$ . **b** Tumor lobules delimited by reticulin fibers. Gomori,  $\times 200$ . **c** Cords of tumor cells in the desmoplastic variant. H&E,  $\times 200$ . (From [2994])



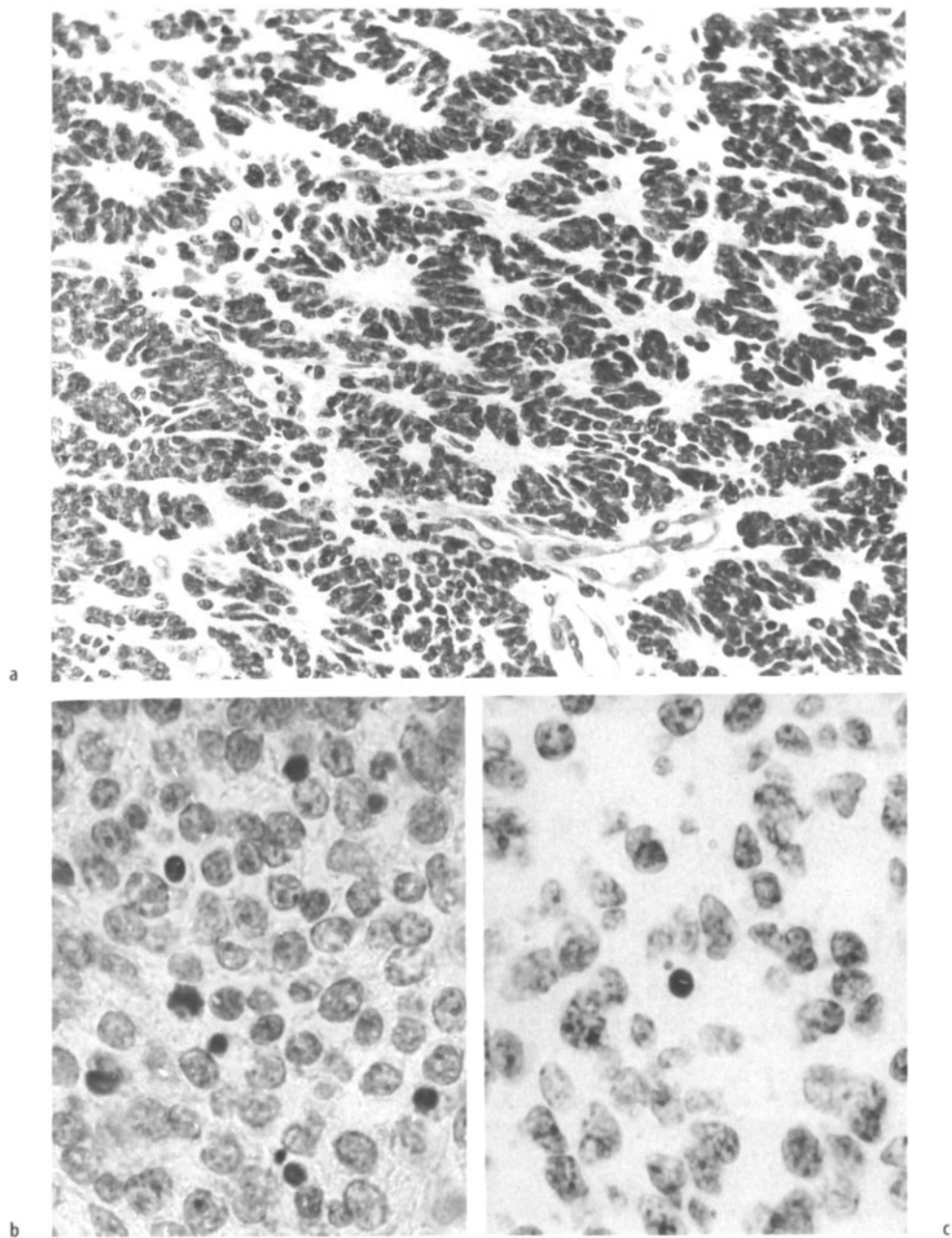
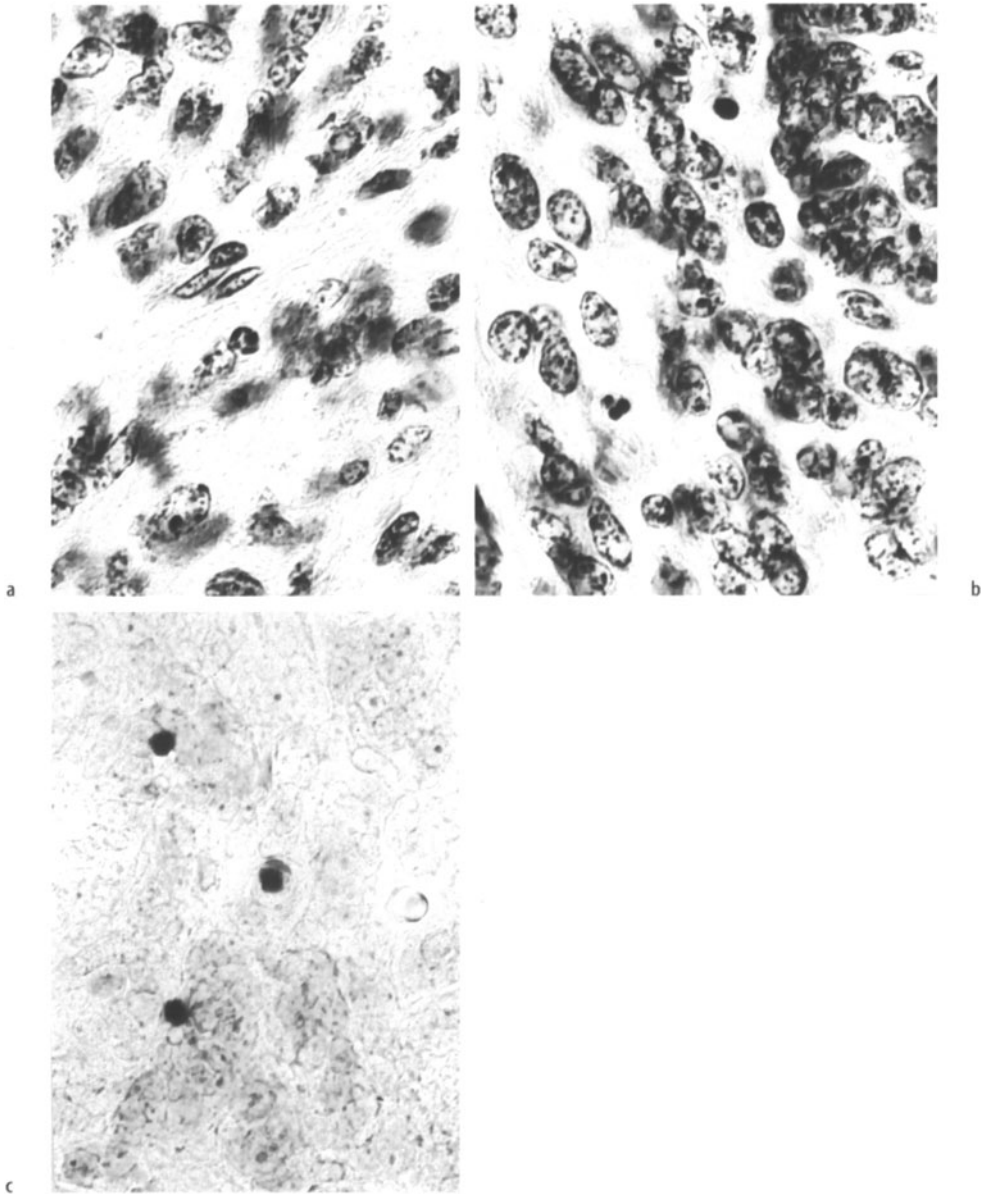
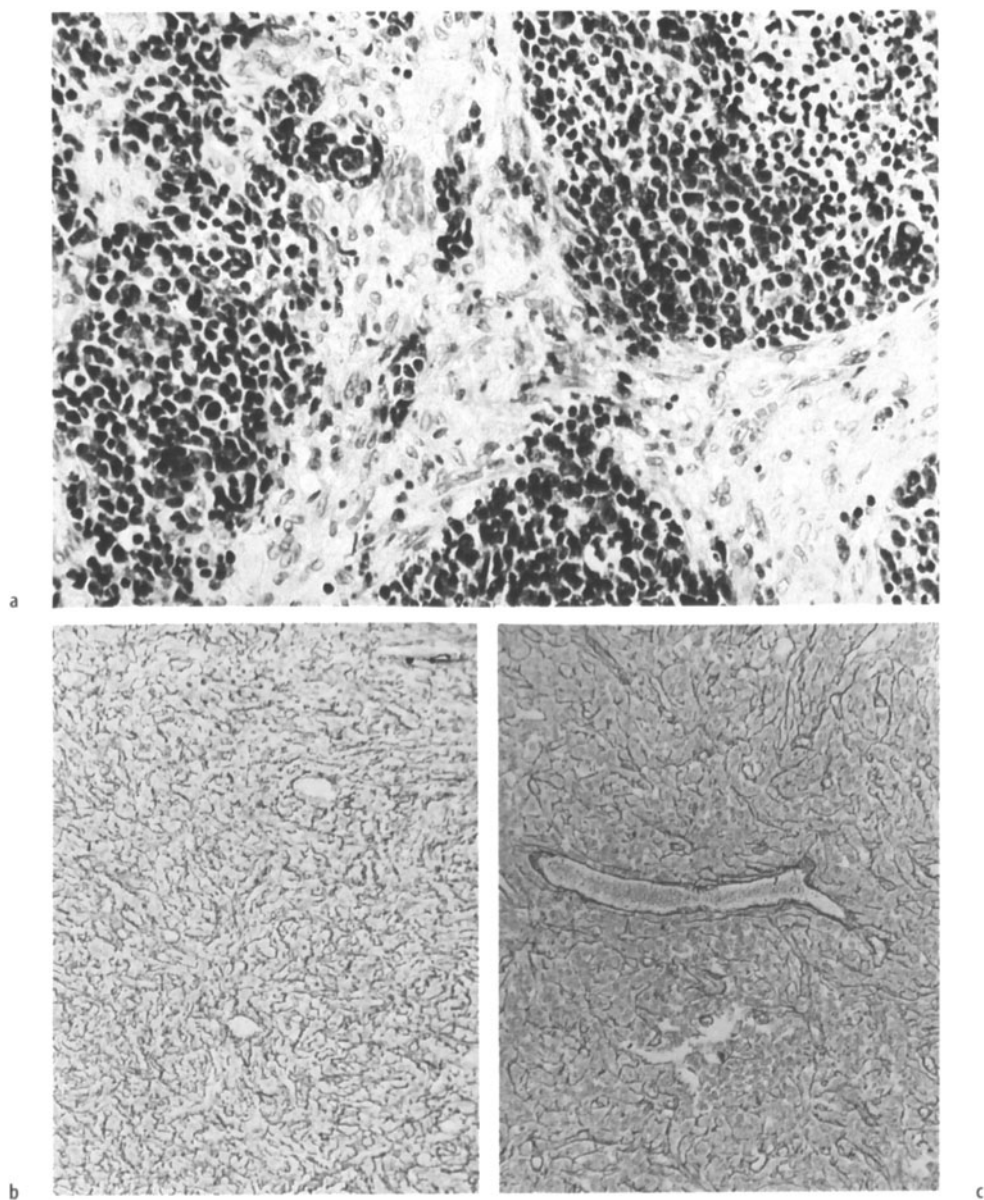


Fig. 15.6a–c. Medulloblastoma. a Homer–Wright rosettes. H&E,  $\times 400$ . b,c Lymphocyte-like nuclei. Carmalum,  $\times 1000$ . (From [2994])



**Fig. 15.7a–c.** Medulloblastoma. **a,b** Apoptotic nuclei. H&E,  $\times 400$ . **c** Apoptotic nuclei. ISEL technique,  $\times 400$



**Fig. 15.8a–c.** Medulloblastoma. **a** Hypertrophic stroma with proliferated vessel walls. H&E,  $\times 300$ . **b,c** Desmoplastic variant with abundant reticulin network. Gomori,  $\times 200$ . (From [2994])

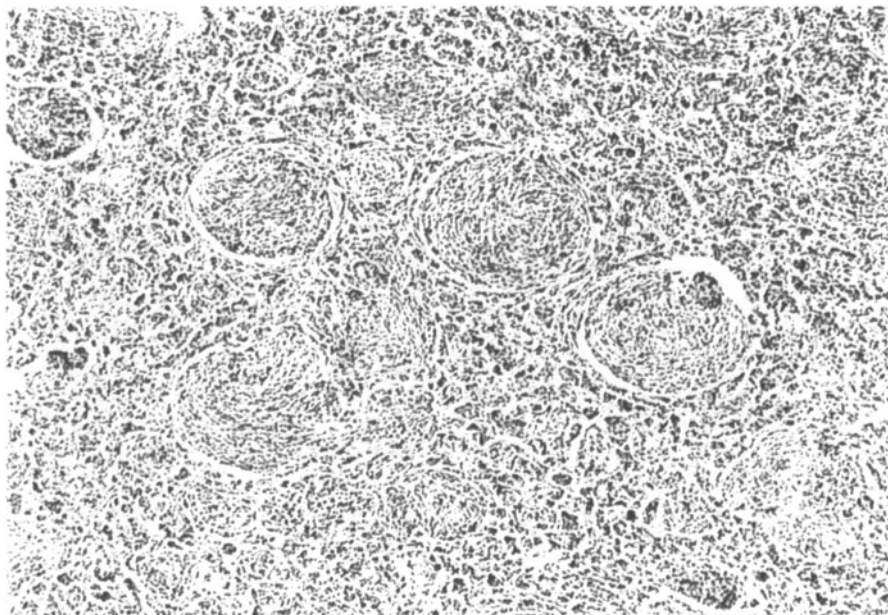


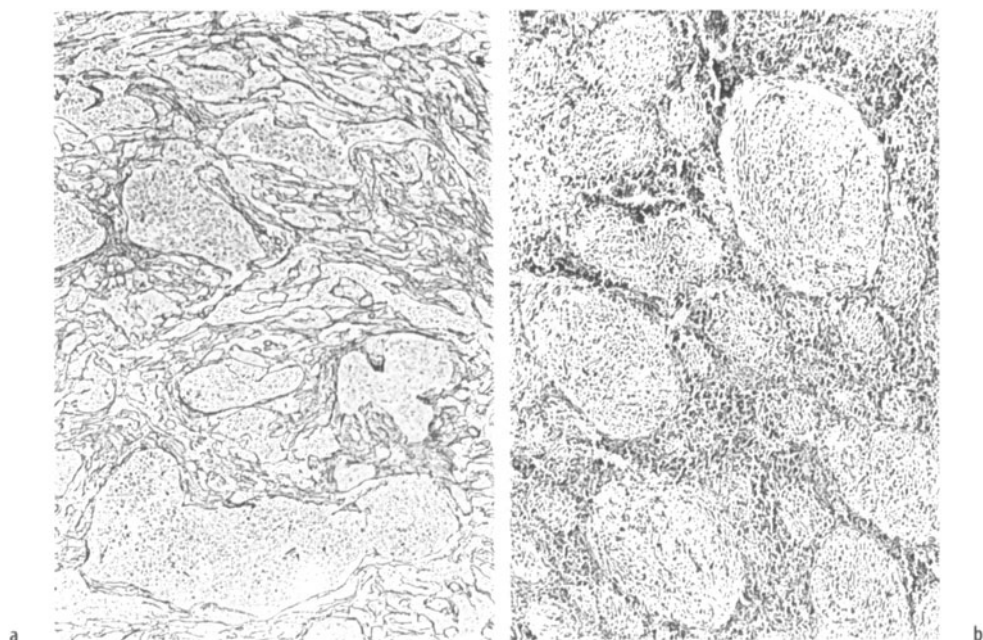
Fig. 15.9. Medulloblastoma, follicles in subarachnoid growth. H&E,  $\times 200$

#### 15.2.3.1

##### *Desmoplastic Variant*

A variety of medulloblastoma is known as “desmoplastic.” It is characterized by growth of the tumor in the meninges so that the tumor acquires a circumscribed appearance and an increased consistency. The location is often lateral. Cords of tumor cells (Fig. 15.5c) are formed which run in parallel with thick, abundant collagen and reticulin fibers (Fig. 15.8b,c). In another mode of subarachnoid growth comparable with the “cerebellar arachnoid circumscribed sarcoma” [920], tumor cells are arranged as mosaics in roundish areas devoid of reticulin but surrounded by rich reticulin strands to simulate reactive follicles of lymph nodes (Fig. 15.9). These go under the name of “pale areas” or “pale islands” (Fig. 15.10), which are considered to be typical features of the variant. Given the importance that the desmoplastic variety has in the biology of the tumor, it is necessary to emphasize that a type of vascular desmoplasia has been recognized [2827], when there is a particular richness in the stroma, even when the meninges are not involved.

Cerebellar neuroblastoma, a variant characterized by lobules of cells immersed in a thin Bodian-positive network and hence formed by neuritic prolongations, has been described (Fig. 15.11b) [3170, 2590, 3739]. The nuclei are vesicular and contain an evident nucleolus, a sign of neuronal differentiation (Fig. 15.11a); sometimes even mature neurons are present [1585, 2903], especially at the edges of the lobules. The distinction between the so-called cerebellar neuroblastoma and the desmoplastic variant of medulloblastoma is not easy because there is not a clear cut separation between the areas described above and “pale areas.”



**Fig. 15.10a,b.** Medulloblastoma, pale islands delimited by reticulin. **a** Gomori,  $\times 300$ . **b** Bodian staining,  $\times 300$

#### 15.2.3.2

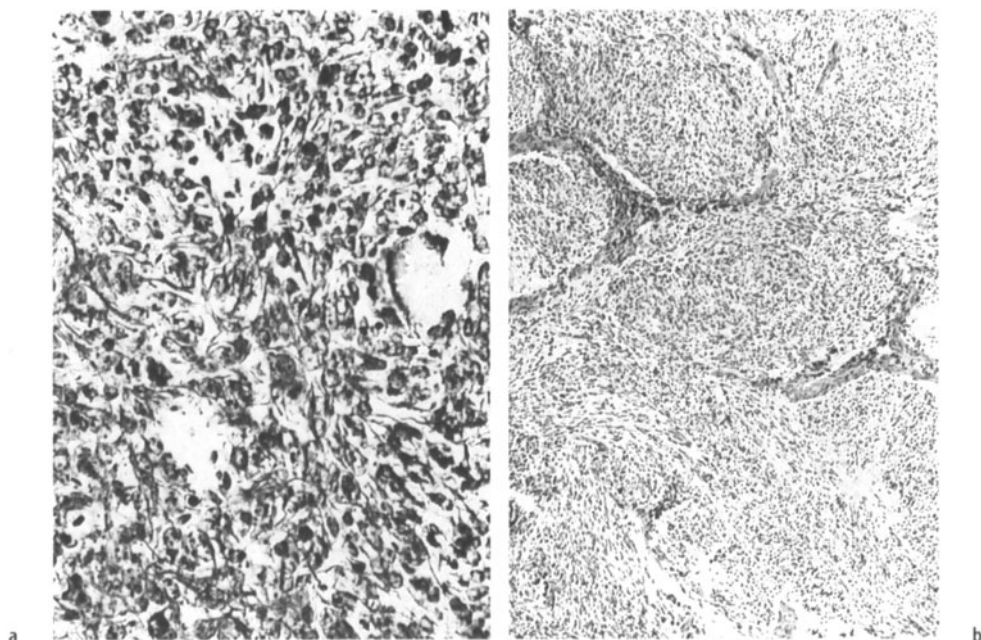
##### *Melanotic Medulloblastoma*

Rarely, and only in children, a pigmented variety has been described [938, 2882, 3343, 226, 285, 767, 747], characterized by cells containing melanin pigment. In general, it is thought that these tumors, usually with neuronal differentiation, derive from the neural crest as the melanotic progonoma, but in contrast to this neoplasm they are malignant.

#### 15.2.3.3

##### *Medullomyoblastoma*

Another variety, containing striated muscle tissue, is known as medullomyoblastoma. Muscle fibers, sometimes abundant, are positive for desmin and myoglobin and under polarized light show the characteristic striations (see Chap. 21). It is thought that the rhabdomyoblastic component derives from the ectomesenchyme, i.e., from the neural crest. The observation that rhabdomyoblastic differentiation occurs in transplants in nude mice from a permanent cell line of a classic medulloblastoma would suggest a neuroectodermal derivation [1070], as has been observed in experimental cultures of gliomas [1917, 1489].



**Fig. 15.11a,b.** Medulloblastoma. **a** Cells with short, positive processes in neuronal differentiation. Bodian,  $\times 400$ . **b** General aspect of differentiated tumors, also called cerebellar neuroblastomas. Bodian,  $\times 150$

#### 15.2.4

##### DNA Content and Pathology

On the basis of microfluorimetric and flow cytometry studies, medulloblastoma has been found to be composed of diploid and, more rarely, of tetraploid cells [1406, 1906, 2323, 3448, 3779, 1009]. Desmoplastic tumors usually have a diploid DNA content. From chromosomal analyses, it has been found that diploid and, more rarely, almost tetraploid cell lines prevail [1880, 250].

Cytogenetic data have been, up to now, limited to a few cases (see Chap. 4). The most common change is the presence of isochromosome 17q [231, 422]; other common changes involve chromosome 1, 6q, 9q, 11, 16q, 17p, or 22 [3493, 2709, 245, 29]. Chromosome 17p contains the gene for p53, which is another gene suggested to be a recessive cancer gene [2194].

#### 15.2.5

##### Problem of Differentiation

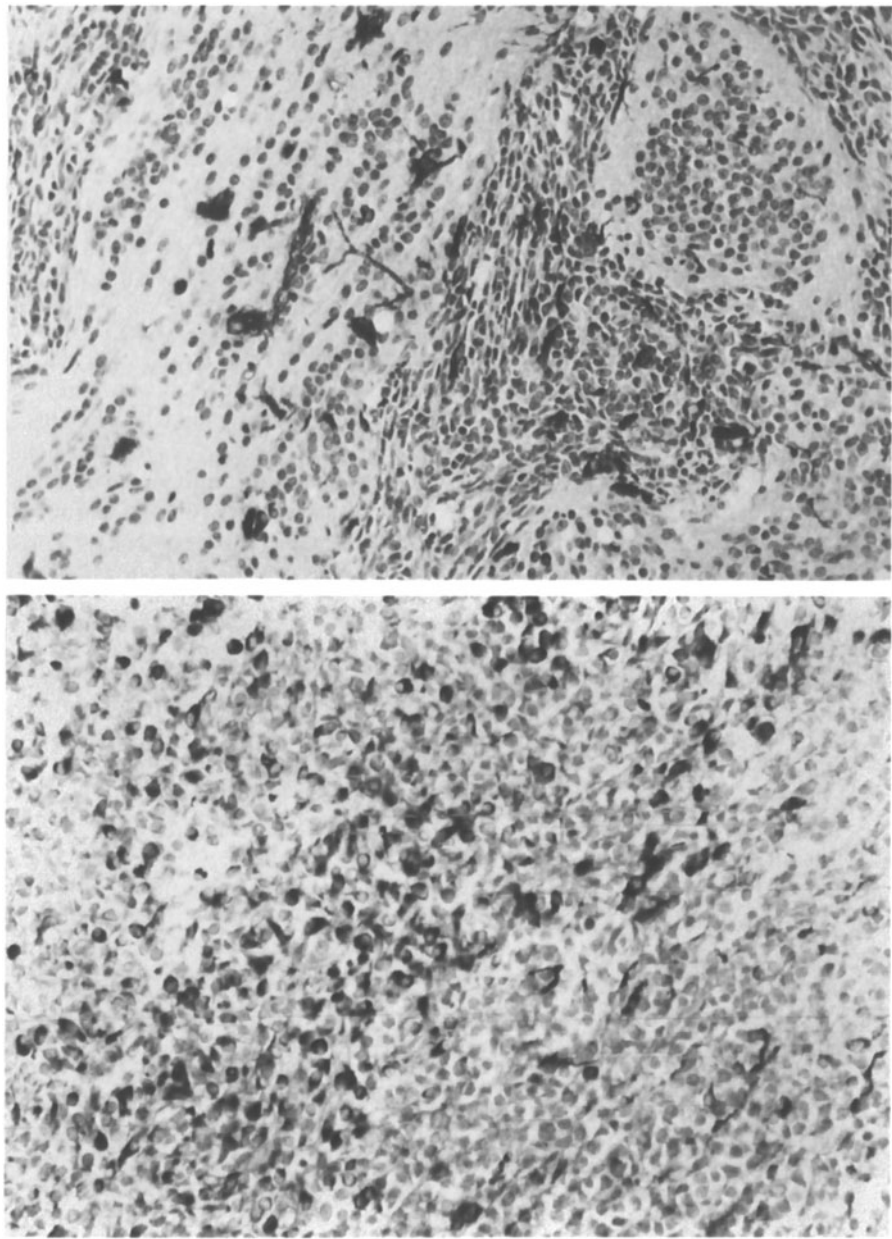
This problem has been debated for half a century and regains strength with each new application of techniques capable of unveiling the glial or neuronal nature of the cells. Basically, it has to be established whether medulloblastoma is an undifferen-

tiated tumor, i.e., formed by primitive, undifferentiated, neuroepithelial cells, or if neuronal and/or glial differentiation takes place. Fifty years of histology, electron microscopy, in vitro culture, histochemistry, and histoenzymology studies have demonstrated, on the one hand, the existence of neurons or neuroblasts and astrocytes and, on the other, that these, were, respectively included in the tumor proliferation, reactive to tumor invasion, or the product of cell differentiation. The whole problem has been reviewed by us up to 1975 [2994]. In the epoche of immunohistochemistry and molecular biology, the debate has gone on with further data, obtained with sophisticated procedures. With immunohistochemical methods, it is possible to demonstrate within the tumor glial fibrillary acidic protein (GFAP)-positive, and hence glial, cells [692, 710, 828, 3507, 668, 3533, 2096, 2550, 1078, 3018, 3042, 1308, 398]. However, they are much more frequent in medulloblastomas in adults [1083].

Depending on the evaluation expressed by various authors on the GFAP-positive cells as tumor or reactive, the incidence of astrocytic differentiation in medulloblastoma may be minimal or absent [540, 3018, 3042], occurring in 50% [2815] or in an even higher percentage of cases [2550]. On the basis of shape, location, and distribution, criteria have been devised to identify GFAP-positive cells as reactive astrocytes or as tumor cells, and hence the expression of glial differentiation by the tumor [2096]. No clear-cut, absolute results have been achieved, the definition of GFAP-positive cells as tumor (Fig. 15.12b) or reactive (Fig. 15.12a) remaining the result of interpretation [613]. In more recent series, it seems that astrocytic differentiation does not occur in more than 10% of cases [1806, 398].

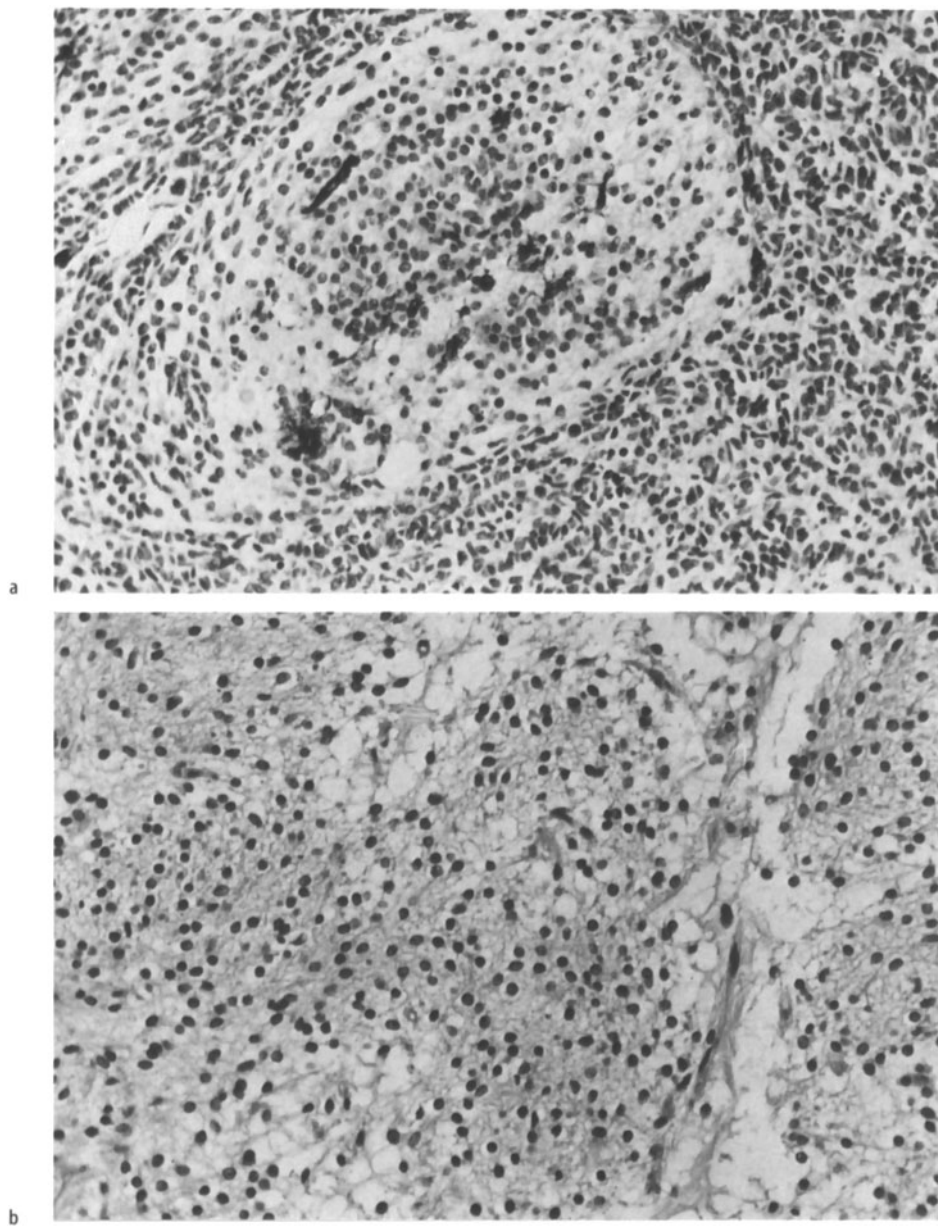
The finding of GFAP-positive cells in the desmoplastic growth is in favor of glial differentiation [1308]. However, opinions are divergent [540, 3042]. Of particular importance is the finding of GFAP-positive astrocytes in the "pale islands" (Fig. 15.13a) [1308, 1605], especially at the border of the reticulin rim, which should resolve the matter because the "pale islands" are only found in the subarachnoid growth and also in the metastases [2882]. However, the doubt that these structures or at least part of them are related to inclusions of healthy cerebellar tissue has not been completely ruled out [3028]. The problem of glial differentiation in medulloblastoma has a theoretical basis, because the external granular layer of the cerebellum does not seem to give rise to neurons and glia, but only to neurons [614, 704], and that medulloblastomas are believed to arise from it [1566, 2876]. However, other structures may give rise to medulloblastoma and are capable of differentiating toward glia before neurons [1945], i.e., the internal granular layer in the roof of the fourth ventricle, which forms the external granular layer, due to dorsal and lateral migration. Medulloblastoma may, therefore, originate in different embryonal periods with different histological features and at different ages of patients [2876]. Under this profile, cases of congenital medulloblastoma are very important (see above). In two recent cases, it has been possible by extrapolating from the growth curves to date the beginning of the tumor to between the 15th and the 24th weeks of intrauterine (i.u.) life [1324], which is the period of the highest histogenetic activity of the cerebellum and in which the cells of the external granular layer are not yet engaged in becoming neurons. The fundamental fact remains that up to now the best demonstration of glial differentiation of this tumor is obtained in culture [1303]. An event that is difficult to ascertain must still be considered, i.e., that glial progenitors are present in medulloblastoma, which still do not express GFAP. In cultures of a medulloblastoma, it has been demonstrated





**Fig. 15.12a,b.** Medulloblastoma. **a** Glial fibrillary acidic protein (GFAP)-positive cells of a reactive nature. **b** GFAP-positive tumor cells. PAP-DAB,  $\times 400$





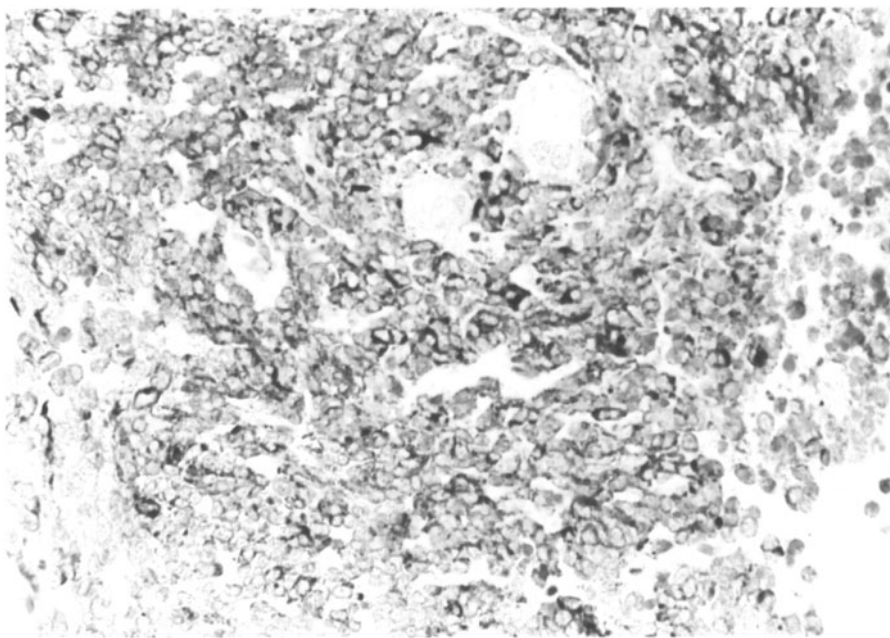
**Fig. 15.13a,b.** Medulloblastoma. **a** Glial fibrillary acidic protein (GFAP)-positive cells in a pale island. PAP-DAB,  $\times 400$ . **b** Oligodendroglial-like aspect. H&E,  $\times 300$

that GFAP expression may be induced in GFAP-negative cells by adding dibutyryl cyclic adenosine monophosphate (dBcAMP) [2110]. This demonstration is a good point in favor of the existence of glial differentiation in medulloblastoma but still does not give sufficient guarantees as to the real existence of glial tumor cells not expressing GFAP, but capable of doing so. Differentiation toward an oligodendroglia line has also been considered, given the presence of "honeycomb" cellular features (Fig. 15.13b) as in oligodendroglioma [2882]. These features may sometimes be found but could be the expression of degenerative events. They have also been interpreted as foci of neuronal differentiation [398].

The problem of glial differentiation is not yet fully resolved. In pale islands of desmoplastic medulloblastoma, GFAP-positive astrocytes have been interpreted as neoplastic [1308], but since they also occur in foci with neuritic cytogenesis they have also been considered as the product of a mutual induction of neuronal-glial differentiation [1605, 1606, 2104]. Cases with glia neoplastic cells are rare, excluding those with gliomatous transformation after irradiation.

The demonstration of neuronal differentiation is better substantiated, if it can be excluded that elements with neuronal characteristics are to be interpreted as normal, included elements, an event which is not at all infrequent, given the mode of growth of medulloblastoma. Electron microscopy data indicating neuronal differentiation are not any more reliable than those indicating glial differentiation [426], even if in some cases electron microscopy has unequivocally demonstrated the neuroblastic nature of the tumor, to the point that these cases were called "cerebellar neuroblastomas" [845, 3170, 1331, 2590, 3739]. Recently, neurite-like processes containing longitudinally oriented microtubules united by "adhesion plaques" have been observed. As in embryonal neurons, they are rich in microtubules and poor in neurofilaments (NF). This would explain the low reaction with the corresponding antibodies. As differentiation proceeds, the NFs increase, and the neurite-like processes elongate, forming the "pale areas," already described [1605]. From the immunohistochemical point of view, mono- and polyclonal antibodies against NF (Fig. 15.14) have not always been used with concordant results [2815, 967, 3534, 398]. In general, the antibodies highlight mature neurons when they are already visible by common histological methods, and therefore, one may be suspicious of their being normal, included neurons. Depending on technical limitations, frequently only neuronal processes can be demonstrated. Neuron-specific enolase (NSE) has been demonstrated to be present sometimes, but it is not completely specific for neuronal neoplasias [1216, 3551]. The conclusion must be made very cautiously; however, it is possible to highlight positive areas which correspond to areas with histological signs of neuronal differentiation [1078, 398].

Focal areas of tumor cells positive for synaptophysin (Sy) have been found in a highly variable percentage of cases [1144, 2269, 3103, 1606, 542], and this antigen has been proposed as a reliable marker of medulloblastoma [542]. More recently, synapsin I proteins, which are associated with the cytoplasmic surface of synaptic vesicles, turned out to give results that were superior to Sy [3235]. The consistent expression of cytoskeletal neuroepithelial markers such as a class III isotype of  $\beta$ -tubulin and microtubule-associated protein (MAP-2) [1605, 1606, 2104, 3552] provide additional evidence of a predominant neuronal differentiation of medulloblastoma, especially in the pale islands of the desmoplastic variant.



**Fig. 15.14.** Medulloblastoma, synaptophysin positivity. (Courtesy of Dr. F. Giangaspero, University of Bologna) PAP-DAB,  $\times 300$

The presence of “synaptic ribbon” type structures, which occur in photoreceptor cells and pineal neoplasms, has also been reported [1303], in line with the immunohistochemical demonstration of photoreceptor molecules [1753, 2614]. Some 35% of medulloblastomas contain the S retinal antigen (SAg), thus appearing capable of a differentiation toward photoreceptors [2610].

Recently, reliable data on the immunohistochemical demonstration of differentiation antigens toward neuronal, glial, or even neuroendocrine lines have become available [2295, 1145, 1244]. Interesting studies were carried out on permanent cell lines, of which four are still continuing. Phenotypic analysis demonstrated that in two of the lines there is a glia-like phenotype [2193, 1490], and in two it was neuron-like [967, 968, 1278]. In the latter, neurofilament subunits of high and medium but not of low molecular weight are produced [3465, 968]. The possibility of rhabdomyoblastic differentiation has already been mentioned [1070].

As far as neuronal differentiation is concerned, more well-founded relationships between medulloblastoma and normal cerebellum development have recently been established. The external granular layer (EGL), which persists in the first postnatal year, consists of a subpial zone with mitotic activity and a subjacent zone composed of postmitotic immature neurons [417]. Both zones are calbindin-negative [1607], whereas class III  $\beta$ -tubulin is positive in the inner zone and proliferating cell nuclear antigen (PCNA) is positive in the outer subpial zone [1604]. It is known that class III  $\beta$ -tubulin is positive only in postmitotic neurons or in neurons in the final mitotic cycle [2301, 1894]. MAP-2, MAP-5, and tau protein show a similar pattern, whereas

no GFAP positivity is evident [3737]. It is very important to note that class III  $\beta$ -tubulin is positive in neurons which derive from EGL, i.e., internal granules and stellate and basket neurons [1607]. Interestingly, calbindin-D28K is absent in EGL and its derivatives and is positive in the ventricular matrix and its derivatives, i.e., Purkinje cells, Golgi II neurons, and deep cerebellar nuclei [1607].

The observation that class III  $\beta$ -tubulin, MAP-2, and tau protein are positive in medulloblastoma [1606, 2104, 2295] is a clear demonstration of the origin of medulloblastoma cells. Based on the expression of class III  $\beta$ -tubulin and PCNA, a gradation of neuronal differentiation in medulloblastoma has been established [1610]. Calbindin-D28K has been found to be positive in medulloblastoma, and it has been hypothesized that classical tumors originate from the ventricular matrix [1604].

As for occasional ganglion cells found in medulloblastoma, an alternative interpretation to their passive inclusion in the tumor is that they represent a Purkinje neuron-like differentiation, an interpretation supported by their positivity for calbindin-D28k. The few tumors containing neurons would be different from desmoplastic medulloblastoma, with a different cytogenesis from the ventricular matrix [1604].

Medulloblastoma is therefore, a truly heterogeneous tumor [1064]. In every day experience, the neuronal differentiation does not seem questionable, since cells with neuroblastic or neuronal features are visible in many tumors with hematoxylin-eosin or Bodian staining, especially when they are in greater number than normal for the cerebellum. Homer-Wright rosettes, which in reality are pseudorosettes because they do not have a real central cavity, are usually accepted as a sign of neuronal differentiation, because of the analogy with the structures in sympatheticoblastomas. The problem of differentiation in medulloblastoma is, therefore, still under discussion, but the occurrence of differentiation is today beyond doubt, especially that toward the neuronal line. It has been demonstrated that there is a similarity between the cytogenetic stages of cells in neuronal differentiation and medulloblastoma cells [3462]. Specific polypeptides such as MAP and NF subunits are similar. In a review of 330 cases, neuronal differentiation was immunohistochemically observed in 60% of cases compared with 13% of the glial one calculated by GFAP-positive staining [1700].

As for the experimental induction of medulloblastoma, JC virus, a human DNA virus of the genus *Polyomavirus*, has been shown to induce medulloblastoma in hamsters. The infected neonatal cells in the external granular layer migrate towards the internal layer and carry the signal of JCV large T mRNA. The origin of the tumor could thus be in the cells of the external granular layer [2378].

### 15.2.6

#### Prognosis, Recurrence, Metastasis

Medulloblastoma grows by infiltration and frequently metastasizes in the nervous system. Metastases normally occur via the cerebrospinal fluid (CSF) and are usually found in the arachnoid, in the vertebral canal, between the spinal roots, in the cauda equina, and on the ependymal surface of the ventricles. Sometimes they may even occur against the flow of CSF. For this reason, the cytological examination of the CSF has taken on a particular importance, especially in relationship to the prognostic evaluation and treatment. Medulloblastoma, together with glioblastoma, is also the

neuroectodermal tumor which most frequently metastasizes outside the CNS [428], probably because of the disruption of the blood–brain barrier (BBB) [2321]. Preferred sites are bones (vertebrae, femur, pelvis), lymph nodes, liver, and lungs [2872, 1709, 2200]. The bony location is responsible for the possible pancytopenia [3276]. The tumor may also infiltrate nearby structures by contiguity, with intradural spread [1501].

The prognosis of medulloblastoma is poor, if not treated, as is that for local recurrence after surgical removal. More than 50 years ago, in the series of Cushing (1930) [624], operative mortality was 32% with an average survival of 5.5 months. Today, 50% of treated patients survive 5 years. Treatment consists in surgical removal, irradiation, and chemotherapy, articulated in diverse protocols of multimodal therapy on the basis of which maximum survival periods of notable duration are obtained [1749, 1873, 275, 854, 3370]. The radiotherapy scheme foresees a tumor dose and an adjunctive prophylactic irradiation to the spinal cord and cerebrum. However, although this regimen may be effective, given the clearly aggressive character of the therapy, deleterious effects on intellectual and somatic development and on the endocrine and hematological functions may appear [779, 1383, 1093]. The problem of therapy of medulloblastoma is thus more complex than that of malignant gliomas of adults.

The dissemination of the tumor via the CSF, even against the flow, has rendered necessary irradiation not only of the tumor focus but also of the brain and spinal cord. One must note, however, that while supratentorial irradiation is responsible for the endocrine and neuropsychological sequelae, the probability of supratentorial metastases is only 8% [1873].

On the basis of Collins' law [553], according to which the period of risk of recurrence is equal to the age at the moment of appearance of the tumor plus 9 months, survival beyond this period is equivalent to cure. Actually, for medulloblastoma there are recurrences well beyond this period. A large number of studies have been dedicated to the identification of prognostic factors, which are essentially age, sex, extent of surgical resection, extension of the neoplasia, histological features, and radio- and chemotherapy. First of all, it appears, not without contradictory data, that an age over 3–5 years and the female sex lead to a better prognosis: 60% against 40% survival at 5 years [218, 2559] or a longer disease-free interval [436]. The extent of the surgical removal is an important factor, because total removal seems to lead to longer survival [2713, 2559, 3444, 1468], but not everyone agrees on this point [436].

The radiation dose to the posterior fossa is also the subject of controversy: while for many authors a dose of 50–55 Gy leads to better survival [218, 1749, 2559, 1907], for others there are no differences to a dose of 40–50 Gy. Given the frequency with which tumor spread occurs in the subarachnoid spaces, the entire craniospinal axis is usually irradiated. The trend today is to lower the dose to the cerebrum in order to reduce the negative sequelae already mentioned [1220].

The prognostic importance of the histological factors is extremely controversial. Individual histological signs do not seem to be important, but some associations are, for example, necroses and numerous mitoses [1749]. Neither proliferation marker LIIs [1475a] nor apoptotic index [3039a] turned out to be prognostic. The favorable prognostic significance of the desmoplastic variant as compared with the classic one, on which many agree, is the object of discussion [2209, 482, 2559]. In striking con-

trast are the results of studies on the prognostic influence of histological signs of differentiation. For some [2525] they did not have any importance, while for others, 72% of patients with such signs were still disease-free after 5 years [436]. In recent series, tumors with neuronal differentiation do not appear associated with a better prognosis [1700], whereas tumors with GFAP-positive tumor cells seem to lead to a longer survival [1119].

The efficacy of chemotherapy is still under discussion [2523, 2532]. In general, it retards but does not prevent recurrence.

The best results are obtained in association with radiotherapy and in recurrences. In association with the postoperative radiotherapy, polychemotherapy (CCNU, vincristine, procarbazine and prednisone) appeared to be efficacious in poor-risk patients (small children, large tumors invading nearby structures, incomplete resection, presence of metastases), even though systematic toxic effects are significant [40, 854, 3370]. In recurrences, various chemotherapeutic agents have been shown to be effective, both singly (high dose methotrexate, cyclophosphamide, cisplatin, carboplatin) [40, 2523] and in combination. Among the latter are eight-drugs-in-1-day [2599], CCNU, vincristine and cisplatin [1903]. Studies are in progress concerning the possibility of reducing the radiation dose to the neuraxis and delaying radiotherapy in small children by preirradiation chemotherapy [1779, 2523].

### 15.2.7

#### Medulloblastoma of Adults

Medulloblastoma in adults is infrequent, accounting for only about 1% of all brain tumors and 8% of posterior fossa tumors. However, 25% of medulloblastomas appear in adulthood, and this seems to be inconsistent with the traditional theory of the embryonal origin of medulloblastoma.

Data on adult medulloblastoma are sparse; they are often included with those of children or concern small series or are collected from different institutions. A slight male predominance is generally reported, and lateral and midline locations are equally represented [1277, 442, 1082A, 975, 2679].

The 5- and 10-year survival rates are within the wide ranges reported for children [442]. No prognostic histologic parameters have been found apart from neuronal or glial differentiation, which turned out to be associated with a worse prognosis [275; 1082A]. Furthermore, the proliferation rates – PCNA and MIB-1 labeling index (LI) – are of no help in predicting prognosis [1082A].

Biopathologic differences seem to exist between medulloblastoma in children and adults: Homer–Wright rosettes and nuclear polymorphism are more frequent in children, while desmoplastic type and glial differentiation are more frequent in adults; the proliferation potential, as revealed by PCNA and MIB-1, is higher in adults than in children [1083]. Cytogenetic peculiarities of adult medulloblastoma have also been found [29].

At magnetic resonance imaging (MRI), the patients presenting with vermian tumors are similar to those seen in childhood, while hemispheric tumors simulate meningiomas or acoustic neurinomas. Hydrocephalus is present in a lower percentage in adult cases than in children [185].

### 15.3 Neuroblastoma

Neuroblastoma is a rare, primitive, hemispheric tumor which arises in children under 5 years old; 26% of sufferers are children under 2 years old [196]. Up to 1976, 12 definite cases had been reported [1395]. Subsequently, single cases have periodically been described, and now their number is over 80 [1018].

#### 15.3.1 Macroscopic Appearance

The tumor is rather large, well-circumscribed, hard, grayish-white, often cystic, and sometimes necrotic or hemorrhagic. It is located (in decreasing order of frequency), in the frontal, parietal-temporal, and occipital areas [1395].

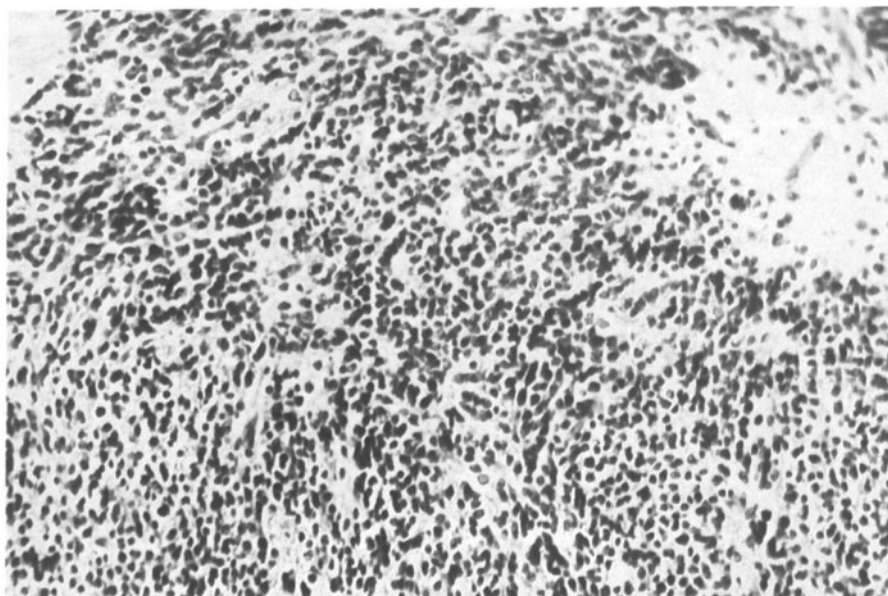
#### 15.3.2 Microscopic Appearance

The tumor is formed by densely packed cells with a hyperchromatic nucleus and numerous mitoses, so that it resembles medulloblastoma (Fig. 15.15a). Three varieties have been distinguished [1395]. In the classical one, the stroma is scarce and limited to blood vessels. The tumor may have a clear-cut limit toward normal nervous tissue or infiltrate diffusely. Homer–Wright rosettes are present, as are sometimes mature ganglion cells (Figs. 15.15, 15.16) (ganglioneuroblastoma). In the transitional variety, the amount of connective tissue is greater, and this is responsible for a lobulated appearance, while Homer–Wright rosettes and mature neurons are less frequent. In the desmoplastic variant there is a compact network of connective tissue with marked lobulation, while Homer–Wright rosettes and mature neural forms are even less frequent. Numerous reactive astrocytes are present around the tumor. The abundant stroma (Fig. 15.17) derives both from the meninges and blood vessels; calcifications are frequent.

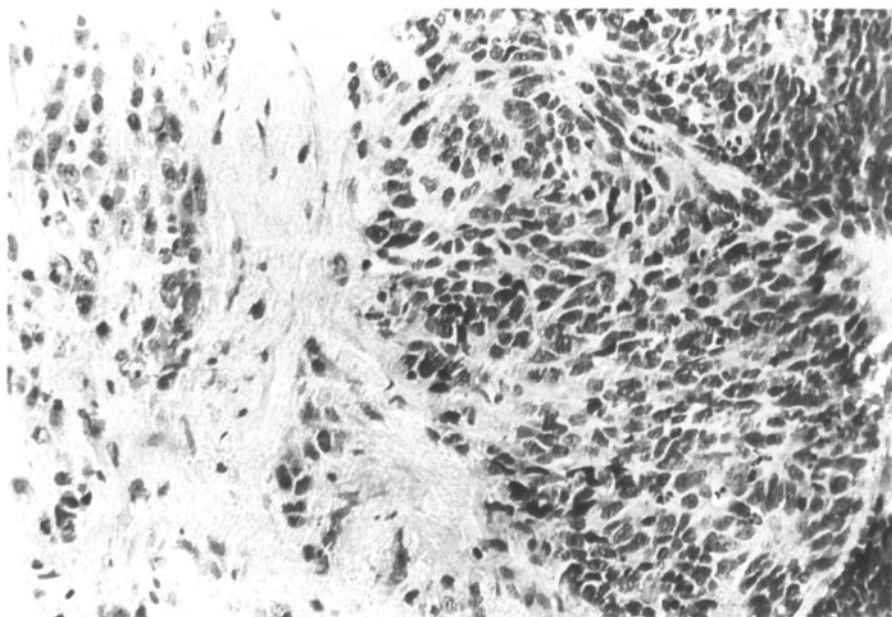
The histological identification of this oncotype is not easy, unless it is possible to demonstrate ganglion and neuroblastic cells and Homer–Wright rosettes, which may be absent or present in variable numbers. If these signs are lacking, the differential diagnosis, especially vs. ependymoma, may be very difficult. In some cases, a palisade arrangement similar to that of polar spongioblastoma has been described [1395, 184, 1863, 2484].

Under the electron microscope, the presence of NF, microtubules, dense core vesicles, synaptic vesicles, junctions, etc. is diagnostic [118, 2774, 1122, 2590, 2484]. It is possible that some of the neuroblastomas, at least those in which neuronal differentiation and the presence of mature synapses extend through most of the neoplasia, could be better labelled as central neurocytoma.

Immunohistochemistry is not of great help, unless an evident neuronal differentiation is present. Positivity for 68-kDa NF has been reported [2815, 1655]. An increased amount of urinary and CSF catecholamines has also been noted [118], but the finding



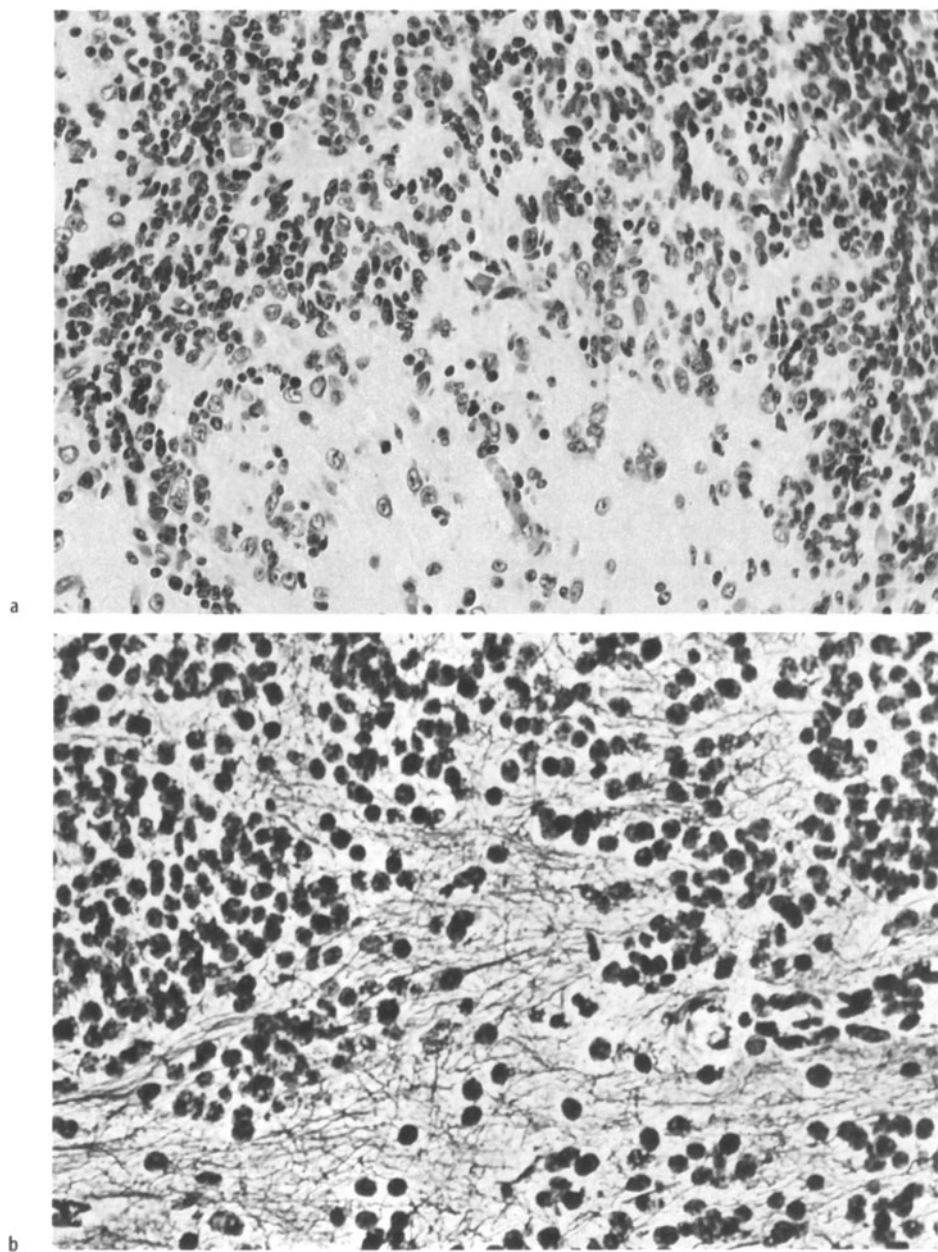
a



b

**Fig. 15.15a,b.** Neuroblastoma. **a** Densely packed cells with hyperchromatic nucleus. H&E,  $\times 200$ . **b** Homer-Wright rosettes and a group of differentiated neurons. H&E,  $\times 400$





**Fig. 15.16a,b.** Ganglioneuroblastoma. **a** Neuroblasts and differentiated neurons. H&E,  $\times 300$ . **b** Differentiated neurons. Bodian,  $\times 300$

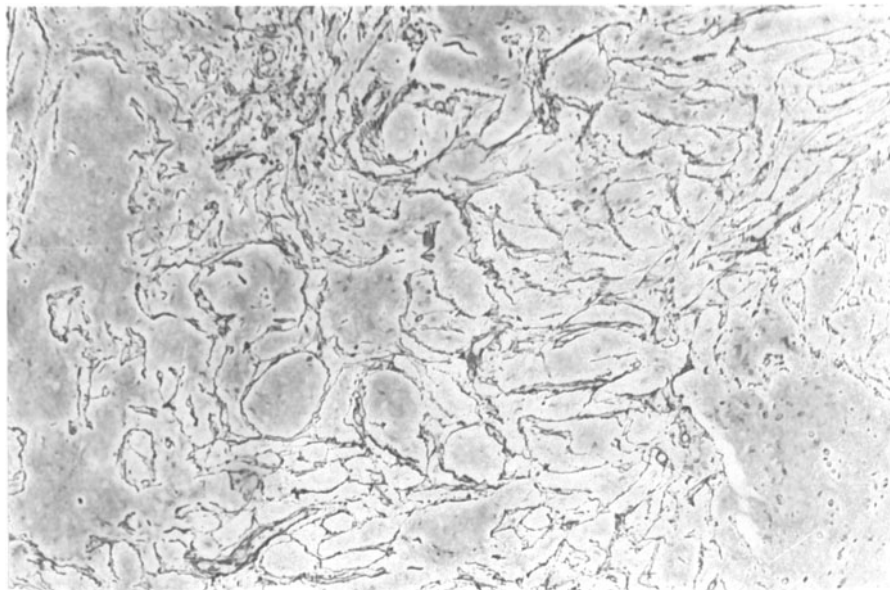


Fig. 15.17. Neuroblastoma, hypertrophied stoma. Gomori,  $\times 200$

has not been confirmed [196]. Cases with differentiation also toward glia have been described [2593, 118, 2921, 649, 2815, 3452], which may support the hypothesis of an origin from a multipotential cell also capable of differentiating toward glia.

### 15.3.3

#### Prognosis

The tumor often spreads via the CSF. Rare cases with extracranial metastasis have also been seen. The prognosis of these tumors is not easy to assess both because they are rare and because of the diverse treatment modalities applied. Prognosis is usually not good, but survival data are distributed over a wide range of periods, i.e., 3 years in 60% of cases and 5 years in 30% [196]. There does not seem to be a relationship between the histological variety and survival [196], even if the cystic forms appear to have a better prognosis [201]. Every so often, cases with a particularly long survival are reported [3452]. Local recurrence, arising in 40% of cases [201, 2904], and metastases along the CSF pathways are the causes of death. The influence of radio- and chemotherapy seems doubtful.

## 15.4

### Polar Spongioblastoma

The term “polar spongioblastoma” has been used in the literature to indicate two types of brain tumors. One is the spongioblastoma group of Zülch [3799], which cor-

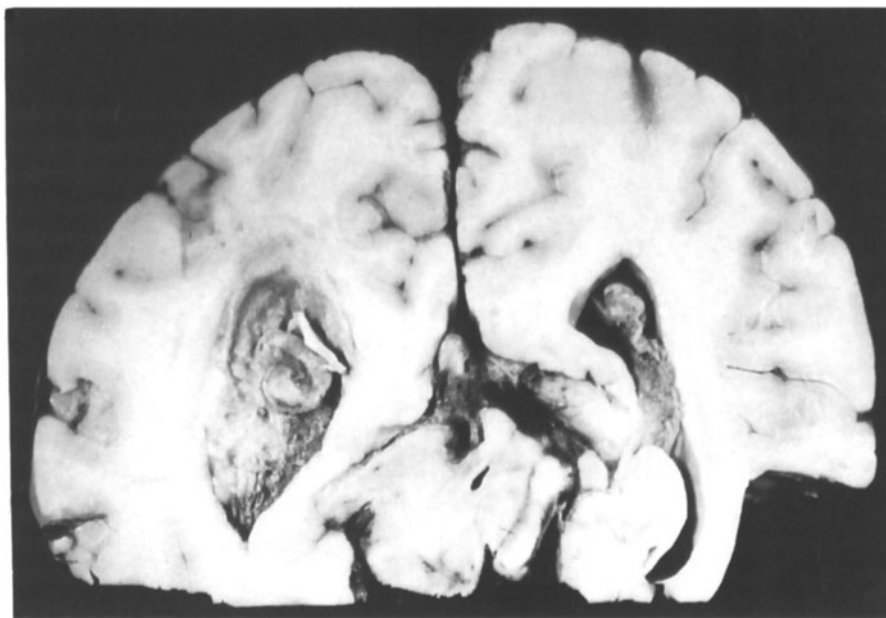


Fig. 15.18. Tumor in the temporal region, diagnosed as polar spongioblastoma

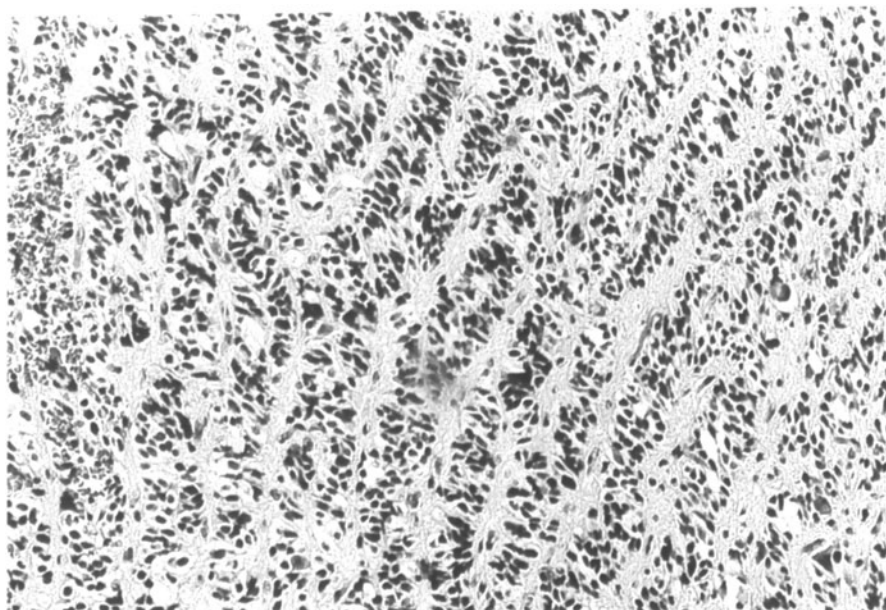


Fig. 15.19. Polar spongioblastoma, typical palisades. H&E,  $\times 200$

responds to pilocytic astrocytoma [2904], and the other is the so-called primitive polar spongioblastoma described by Russell and Cairns [2898] and by Russell [2897] as a malignant brain tumor arising in the neighborhood of the ventricular system mainly in childhood and adolescence. A few examples have been reported from different locations: the cerebellum [1910, 3301], mesencephalon [2898], fourth ventricle [2898], diencephalon [671], frontal lobe [1509], temporal lobe [2899], and spinal cord [3221, 3071] (Fig. 15.18).

Histologically, the tumor is composed of poorly differentiated cells with nuclei arranged in a parallel fashion forming typical palisades (Fig. 15.19). Cellular layers and groups are separated by a vascular-connective stroma. The cells have a polar shape and delicate fibrils. The authors who originally described the tumor thought that the cells were undifferentiated, but capable of differentiating toward glia or oligodendroglia. The cells are GFAP-negative.

The controversy about this tumor revolves about whether it is a real entity or simply a particular form of glioma. In the cases so far published, besides the spongioblastic aspect there was also an astrocytomatous aspect [662, 3071, 3301] or an oligodendrogliomatous one [2868]. Those who believe the tumor is an entity consider the latter aspects as differentiations of an immature tumor. The nonbelievers think that, on the contrary, the spongioblastic aspect is an epiphenomenon.

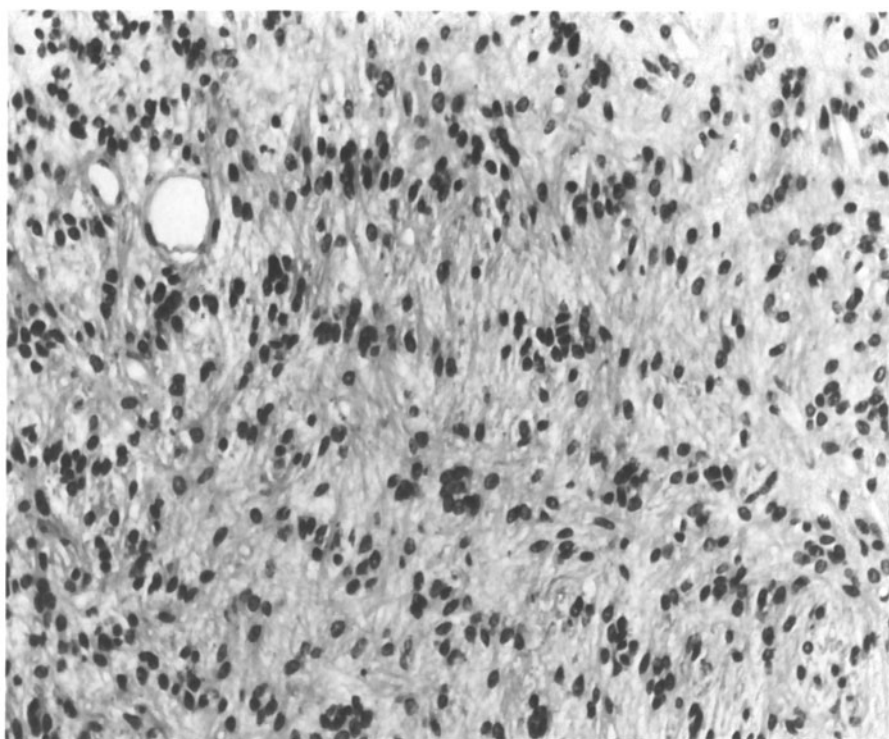
In some neuroepithelial tumors, such as cerebellar astrocytomas, (Fig. 15.20a), ependymomas (Fig. 15.20b), oligodendrogliomas (Fig. 15.21), and even medulloblastomas, areas with palisadings or rhythms of nuclei can be found. Palisadings have also been described in neuroblastomas [1863, 184], but there they are separated by reticulin bundles [1395]. In the personal series, two cases with a typical spongioblastic aspect were found. Both tumors were located deep in the temporal lobe, of a 12-year-old child and a 51-year-old woman. Delicate fibrils were evidenced by phosphotungstic acid-hematoxylin (PTAH); GFAP was negative and vimentin was positive, which might have some relevance to the immaturity of the tumor. Calcifications were present as well as mitoses and circumscribed necroses. The tumor behaved malignantly and both patients died 3 years later. In one case, the tumor showed (under the electron microscope) characteristics of a neuroblastoma with microtubules and dense core vesicles (Figs. 15.22, 15.23); in the other, after serial sections a typical ependymomatous aspect was found in a circumscribed area of the tumor. A case with clear-cut neuroblastic characteristics was reported recently [1509], and neuroendocrine aspects have been observed in another instance [671].

Palisadings are not uncommon in neuroepithelial tumors, where they represent the secondary architecture. In a few instances, the polar spongioblastic aspects may represent the primary architecture and characterize the extension of the tumor. This happens mostly with neuroblastomas and ependymomas to which the so-called polar spongioblastoma belongs.

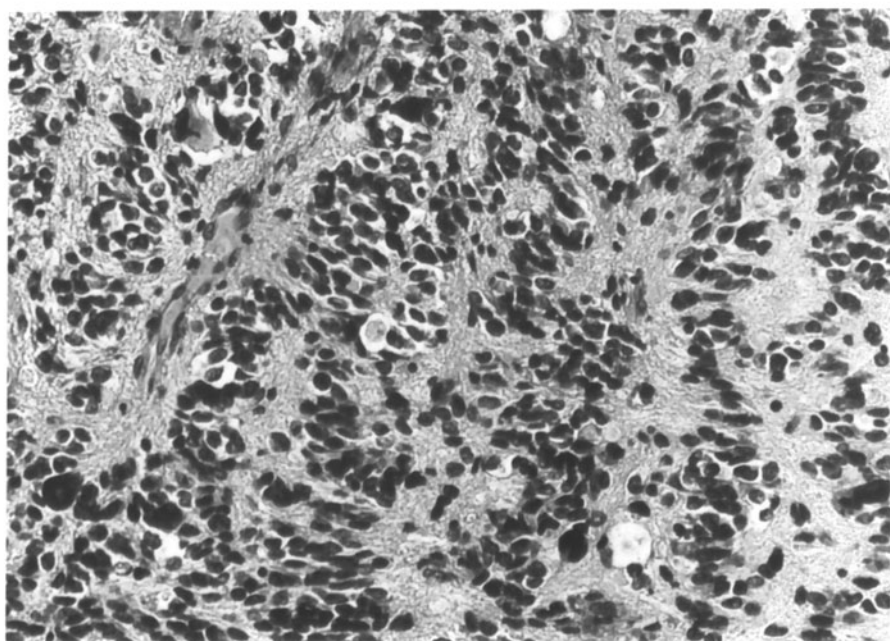
## 15.5

### Appendix: Tumors of the Retina

Embryologically speaking, the retina originates from an extension of the primary cerebral vesicle. From the complicated anatomy of the invaginated optic cup, two im-



a



b

portant features must be stressed which have a prominent relationship with tumors arising from this structure. First of all, there are the pigmented elements of neuroepithelial origin, interposed between the layer of cones and rods and that of the choroid; other pigmented elements, of mesenchymal origin, are those of the choroid layer. The rod and cone layer corresponds to the ventricular endyma. It may react to pathological processes, forming rosettes. Beside neurons, which are the photoreceptor cells, the retina contains glia cells which are represented by Müller's cells and by stellate astrocytes.

### 15.5.1

#### Retinoblastoma

Retinoblastoma originates from immature retinal cells and is the most frequent malignant ocular tumor in childhood. The average age of the patients at clinical diagnosis is 18 months [2864]. Very important to note is that the tumor is heritable in 40% of cases. It is heritable in all cases where it is bilateral and in 10%–15% of unilateral cases. Conversely, all nonheritable cases are unilateral.

Molecular genetic studies have demonstrated that the tumor results from two mutational events (see Chap. 2). In the heritable form, the first mutation on the RB gene is transmitted by the germinal cells, while the other occurs in the somatic cells; in the nonheritable form, both mutations occur in the somatic cells, the first before birth and the second after birth [2127].

Secondary malignancies may develop in the heritable group of patients, represented mostly by osteogenic sarcoma, in 15%–20% of patients after a mean interval of 11 years [5]. A debate arose about the possibility that such malignancies could be due to the radiation therapy.

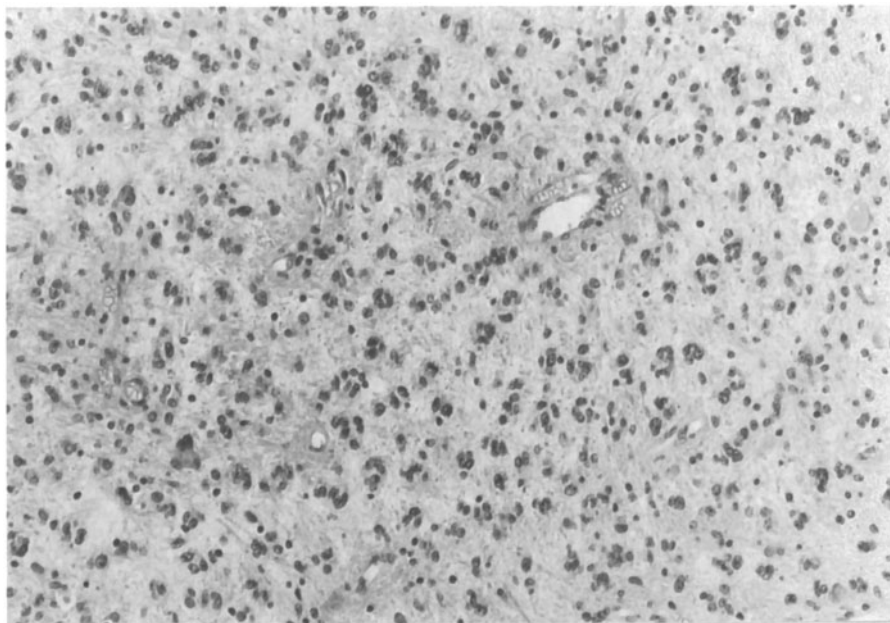
Another association of bilateral retinoblastoma is that with pinealoblastoma, the so called trilateral retinoblastoma.

Macroscopically, the tumor appears at an early stage as a white nodule in the posterior part of the retina. It grows by detaching the retina or forming masses in the vitreous chamber. Finally, the globe enlarges, and the tumor may extend through the sclera.

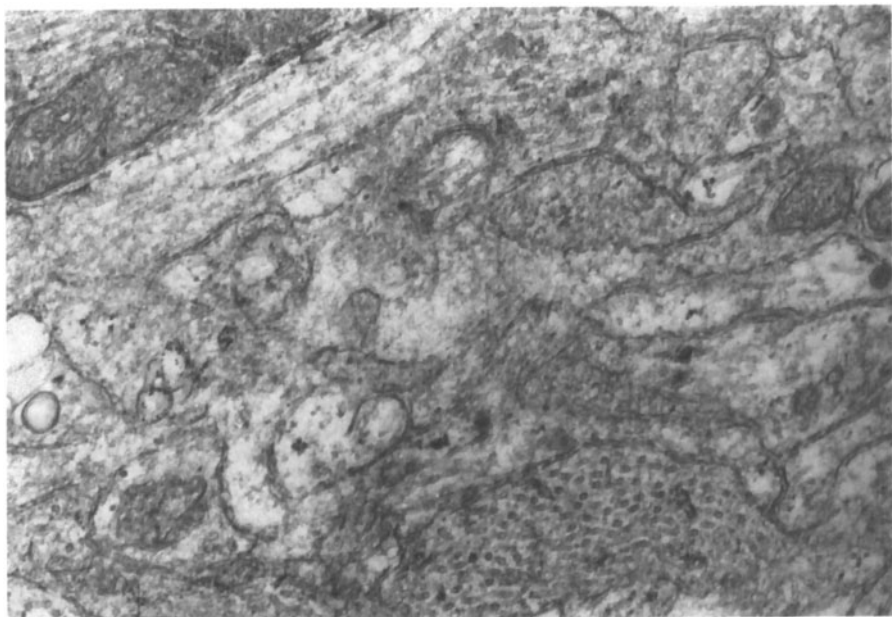
Microscopically, the tumor reveals a high cell density. The cells are round or oval with scanty cytoplasm and large nuclei. Many mitoses are present. In most cases, rosettes are found (Fig. 15.24): Cells, often in mitosis, are arranged about a lumen to which stretch the cytoplasm covered by a membrane stained with PTAH. Fleurettes may develop [3468] as a sign of photosensory differentiation, formed by long processes traversing a membrane side by side. Occasionally, Homer–Wright rosettes can be found.

A matter of lasting debate is the occurrence in the tumor of a glia differentiation. Some interpret the GFAP-positive glia cells occurring in the tumor as reactive gliosis [2616], whereas others believe that they are an expression of a glial differentiation [3414]. The real occurrence of such differentiation still remains controversial [2904].

◁ Fig. 15.20. **a** Step-ladder rhythms in pilocytic astrocytoma. **b** Step-ladder rhythms in ependymoma. H&E, ×300



**Fig. 15.21.** Cell rhythms in oligodendroglioma. H&E,  $\times 300$



**Fig. 15.22.** Polar spongioblastoma, interdigitating cell processes and microtubules. Uranyl acetate, lead citrate stain,  $\times 40\,000$



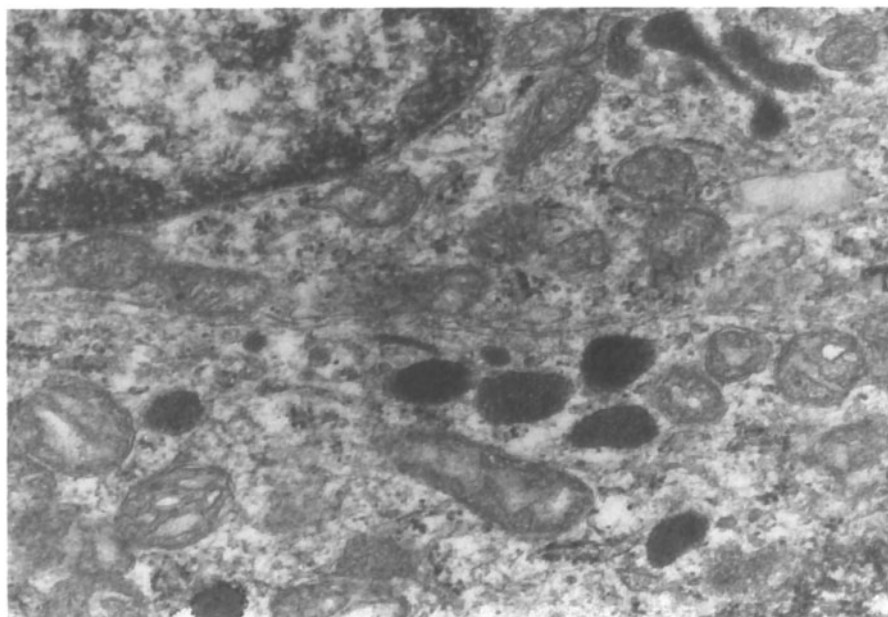
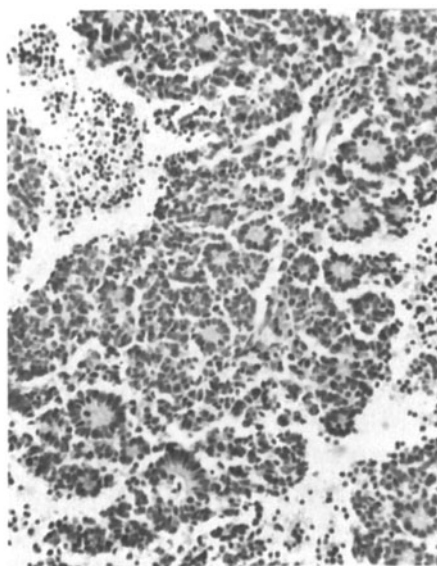
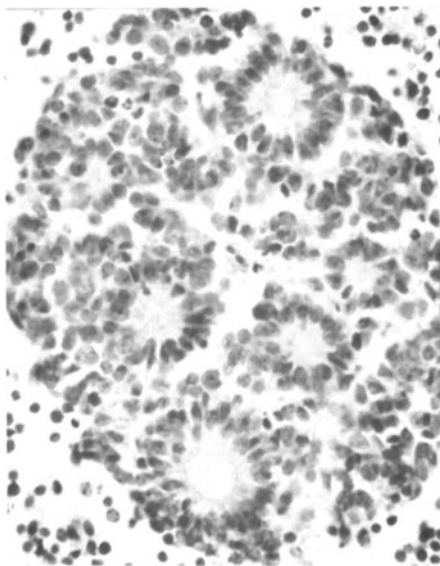


Fig. 15.23. Polar spongioblastoma, dense core vesicles. Uranyl acetate, lead citrate stain,  $\times 40\,000$



a



b

Fig. 15.24a,b. Retinoblastoma, typical rosettes. H&E, a  $\times 200$ , b  $\times 400$



Electron microscopy demonstrated photoreceptor differentiation, fleurettes, cilia with a 9+0 pattern, synaptic ribbons, and dense core vesicles but was unable to settle the controversy about glia differentiation [26].

The same interpretation given to the GFAP positivity, i.e., as due to reactive glia cells, could be applied to the positive staining for S-100 protein observed by some [1694] and anti-Leu 7 [2616]. The positive staining for NSE, found by many, must be considered with reservation because of the poor specificity of this marker. Flexner's rosettes were positive for 68- and 210-kDa subunits of NF [2960]. Also positive is the staining for S antigen in rosettes, fleurettes, and isolated cells [753, 2616], as well as for rhodopsin [754].

Retinoblastoma cells have been grown in culture, and some established cell lines are available. Data on the cell kinetics show high values for the LI.

Retinoblastoma is a malignant tumor, but in most cases the treatment is highly effective: The cure rate is almost 90% [26]. Distant metastases are rather rare. Also rare, but possible, is its spontaneous regression.

## Glomus Tumors, Paragangliomas

Paraganglia have been divided [3619] into sympathogenic chromaffin and parasympathogenic nonchromaffin. The former derive from the adrenal medulla, the so-called free paraganglia, and some intraneural or intraganglionic chromaffin cells, from which chromaffin paragangliomas such as pheochromocytoma arise. The latter are represented by collections of epithelioid cells situated on the blood vessel wall in relation to the vagus and glossopharyngeal nerves. They go under the name of carotid, jugular, tympanic, vagal, aortic, and supracardiac paraganglia. Related tumors are glomus tumors or nonchromaffin paragangliomas or "chemodectomas" [2356]. An objection to the last nomenclature is that there has been no definitive demonstration of chemoreceptor function in these tumors [1095]; thus the term paraganglioma which may be specified as functioning or nonfunctioning, is preferable.

It is possible to demonstrate biogenic amines using formaldehyde-induced fluorescence in all the paraganglia.

### 16.1

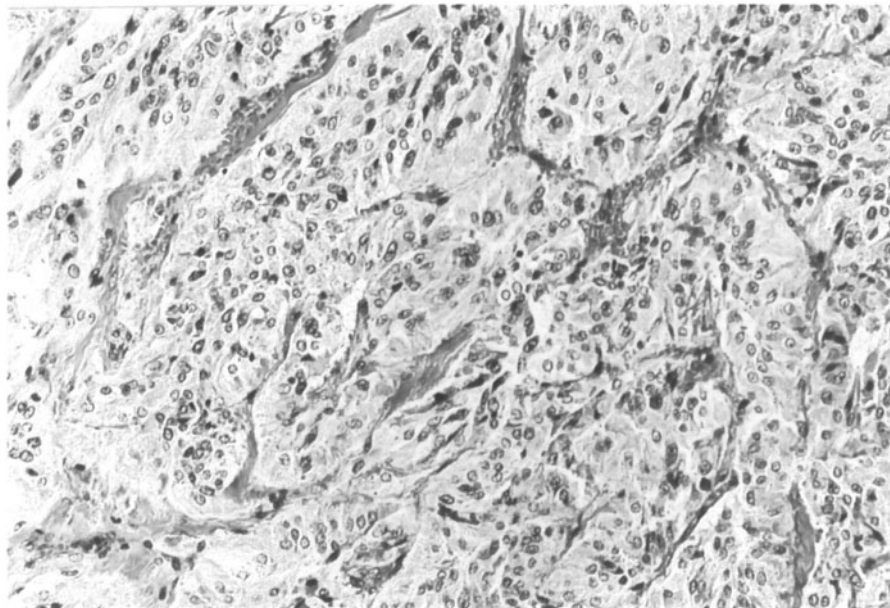
#### Site, Age, and Clinical Features

They are rare tumors. Some have been described as located in the head and neck [3083, 550, 1287] with 160 cases having been reported by 1957 [1712], whereas spinal tumors are very rare, only 11 cases having been described by 1984 [2266, 1919, 1388, 3499, 2903, 1841, 273, 1993, 3061, 3403, 1455].

Another seven cases have been successively presented [292], of which three were epidural and four intradural. Recent series, especially from laryngologists, are more numerous [354, 800].

Only five tumors have been described in the cauda equina, and some in the orbit [2432, 3537, 2582]. In general, the sites along the cerebrospinal axis at which the tumors have been reported include the pineal gland, the pituitary gland, and the cauda equina. They often appear at multiple sites, and sometimes in other members of the family. The age of predilection of these tumors varies between the fourth and the sixth decades of life. Females are more often affected.

Bilateral or multicentric glomus jugulare tumors have been described [2496]. Patients with such tumors or with a positive family history probably have genetic disorders. The predisposition to develop such tumors is in some cases inherited as an autosomal trait on chromosome 11q 23qter. However, tumors seem to develop only when the mutant gene is inherited from the father. It is speculated that the gene acts



**Fig. 16.1.** Paraganglioma, lobules and cords of roundish cells delimited by a connective stroma. H&E,  $\times 300$

as a tumor suppressor gene, inactivated during oogenesis and inherited as nonfunctional from the father [3508].

Symptomatology depends on the location, including hearing loss and ear symptoms for tumors within the middle ear. Multiple cranial nerve deficits follow with Vernet or Billaret syndrome, i.e., loss of function of cranial nerves IX, X, and XI or IX, X, XI, and XII, together with Horner's syndrome.

## 16.2

### Macroscopic Appearance and Imaging

Computed tomography (CT) and magnetic resonance imaging (MRI) are helpful, but frequently not conclusive. Glomus jugulare tumors are laterally located and involve the middle ear. When they enlarge, they either extend through bony canals or produce erosion of the petrous bone and can reach the cerebellopontine angle.

In the spinal canal, the tumors show a delicate capsule and may be attached to the filum terminale or to the nerve roots. In other sites, the aspects are variable.

In glomus tumors, angiography is mandatory, especially because if a feeding artery is visualized, embolization is usually carried out before surgery.

### 16.3

#### Microscopic Appearance

Histologically, they are characterized by tufts of roundish or elongated cells with abundant eosinophilic cytoplasm, immersed in a connective stroma rich in blood vessels (Fig. 16.1). Three types have been described [1889]: a typical one with an “organoid” arrangement in which the cells are enclosed between vascular and sinusoidal channels [1095]; an adenomatous type with features closer to epithelium; and the angiomatous type with particular prominence given to the vascular network. On this histological appearance there is agreement among various authors [1712, 3431, 2648]. The main cells of a juxtacarotid chemodectoma cultured *in vitro* are bipolar, one of the poles being nuclear and the other cytoplasmatic, as in histological preparations [579]. The cells may give off a process which grows in a way similar to an axon; they do not actively migrate, but the body shows pulsatile contractions. Cells with cytoplasmic argyrophilic granules situated at the periphery of the lobules have been observed in many tumors. In culture, however, these cells are not easily recognized. Bundles of nerve fibers related to the blood vessels are present in these tumors, but they are not observed in culture.

The argyrophilic cells of the tumor are thought to be similar to those of the gastrointestinal tract and may secrete serotonin. This would agree with the fact that the histological structure of the organ is that of a highly specialized neuronal photoreceptor. Under the electron microscope, dense core vesicles and secretory granules are recognizable [1455]. The cells are positive for chromogranin.

Rare cases containing melanin have been described, two in the uterus [3400] and one in the orbit [2582]. Positive staining for GFAP and S-100 protein in sustentacular cells was found in many cases of 65 adrenal and extra-adrenal paragangliomas and was correlated with a good prognosis [7].

### 16.4

#### Prognosis

Paragangliomas grow slowly but may invade the surrounding structures, especially the blood vessels. They may also show extracranial extension [3179] or compress the brain stem and cerebellum. Rarely, extracranial metastases are observed [3697, 1882, 2845].

The elective treatment is surgery, even though a complete resection is rarely possible because of the invasiveness and location of the tumor. The tumor often recurs [2747]. Radiotherapy as primary or postsurgical treatment leads to contrasting results [98, 3198, 1672, 2251]; it does not “sterilize” the tumor [3268]. In cauda equina tumors, the prognosis is good in the case of total removal, unless lymph node involvement and distant metastases appear [2765].

In addition to surgery, radiotherapy or radiosurgery is recommended. The outcomes after different procedures are still the subject of heated debate.

## Tumors of the Cranial and Spinal Nerves

### 17.1

#### Neurinoma (Schwannoma)

This tumor has been given various names, due to the various cells of origin proposed. Some authors have postulated a fibroblastic origin for the tumor cells, while others have proposed an origin from Schwann cells. The term “fibroblastoma perineurale” was coined by the former authors to indicate an origin from the fibroblasts of the perineurium [2083, 2601], although later on the derivation was thought to be from the endoneurium [3397]. The term “neurinoma” or “neurofibroma” was used by other authors [1394] to underline its neuroectodermal nature. The term “neurilemmoma” has been used to emphasize its origin from Schwann cells [3320]. Today, there are no doubts as to the origin of these tumors, and the most frequent label is neurinoma in Europe [3799] and schwannoma in the USA [2904].

It should be noted that the two theories on the origin of the tumor are not mutually exclusive: From the basic concept of “mesectoderm” it is possible that the primitive neural crest gives rise to both Schwann cells and mesenchymal perineurial cells [1195], and observations on the mesenchymal origin of Schwann cells have been made [874].

The problem of the relationship between neurinomas and neurofibromas, especially when multiple as in neurofibromatosis, is somewhat complex. For the latter tumors, investigators are divided between a mesodermal (fibroblasts originating from neural connective tissues) and an ectodermal (origin of the tumors from Schwann cells) interpretation.

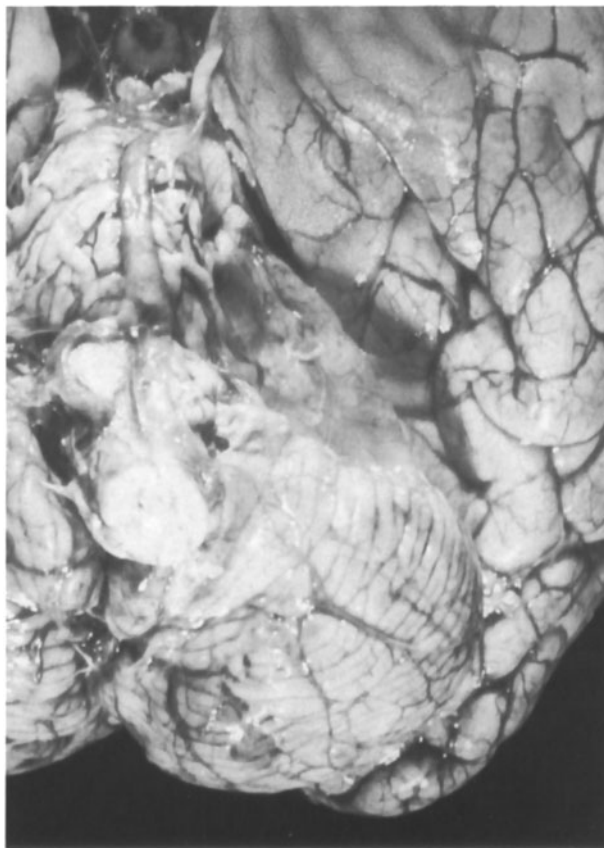
#### 17.1.1

##### Frequency, Age, Sex

Neurinomas represent around 6.8% of all brain tumors, but at the spinal site they are more frequent than meningiomas, representing 25% of all tumors [3803]. Neurinomas of the peripheral nerves are very rare.

They more commonly occur in the fourth and fifth decades, and the average age is slightly lower for spinal tumors. Neurinomas are truly rare in childhood.

There is a greater incidence in women.



**Fig. 17.1.** Neurinoma, tumor bed in the cerebellopontine angle

### 17.1.2

#### Site

The most frequent site of origin is the cerebello-pontine angle, followed by the spinal cord. In the former, the tumor arises from the eighth nerve, more precisely from the vestibular component, close to or in the ganglion of Scarpa. It arises from both the superior and inferior vestibular nerve. It then involves the acoustic component, the facial nerve in the internal acoustic meatus [1295, 1296, 1236], and spreads into the cerebello-pontine angle (Fig. 17.1). The tumor may burrow into the medulla, pons, or cerebellum (Fig. 17.2). It may extend inferiorly to the foramen magnum, and superiorly through the tentorium. It usually engulfs the fifth and sixth cranial nerves. The tumor is usually unilateral but can occasionally be bilateral, normally in the context of neurofibromatosis.

In the cerebello-pontine angle, many tumor–cranial nerve interfaces must be considered from the surgical point of view; a cleavage plane must be found, first of all with the facial nerve. In large tumors, however, the latter cannot be spared. It has been demonstrated that in these cases there is no clear-cut histological cleavage



Fig. 17.2. Neurinoma, tumor burrows in the pons and cerebellum

plane. Nerve fibers abut directly against tumor cells and penetrate into the tumor [1483].

More rarely, neurinomas may arise from other cranial nerves. The most common site is the trigeminal or the Gasserian ganglion, but most of these tumors occur in cases of neurofibromatosis. Isolated neurinomas of the fifth nerve have been reported by various authors, and 61 cases, personal and from the literature, were reviewed in 1960 [3043]. Further cases have been described since [306]. Those arising from the ganglion, the majority, are usually kept separate from those of the roots.

Neurinomas of the seventh nerve are next in order of frequency. They may arise from the intracranial portion of the nerve [1001, 194, 1893], but more often they develop from the intratemporal part, and even extratemporally and extracranially. Forty cases had been published before 1959 [1713]. A case in the labyrinth has been reported [1959].

Neurinomas of the twelfth nerve are even rarer [3683, 2310, 163], amounting to no more than 34 cases up to the end of 1989 [2472]. Neurinomas of cranial nerves IX, X, and XI are very rare [1219], and up to the end of 1989, 100 cases had been reported, 23 of which were on the ninth nerve [3346]. Theoretically, the tumor may arise at any intracranial site, for example, cases of the fourth cranial nerve have been reported [289, 1344]. They may very rarely be found at sites distant from the cranial nerves, in the sella [1109, 3681], in the frontal region, extracerebrally [3527, 2177], or

within the neural parenchyma [362, 3292, 610, 2904], as part of von Recklinghausen's disease. They may arise either from small nerves in the meninges or from ectopic Schwann cells.

The spinal tumors mostly arise from the sensory roots and are often situated dorsally or dorsolaterally to the cord. Sometimes, it is difficult to ascertain from which root they arise. There is no particular predilection for a given spinal level. The thoracic or lumbar roots are probably the ones most affected. The position of the tumor in relation to the dura assumes a particular importance in the spinal canal. The majority of neurinomas are intradural, but some are extradural or are both intra- and extradural. The latter are named "dumbbell" tumors because, after arising intradurally or at the transition between the intradural root and the extradural nerve, they cross the intervertebral foramen and assume this particular shape. In a series of 163 cases [2738], 67% were intradural, 16.5% extradural and 16.5% both intra- and extradural. In another series of 266 cases [1660], 176 (66%) were intradural, 45 (17%) were extradural and 45 (17%) "dumb-bell" tumors. Conversely, 48% of spinal dumb-bell tumors (34/73) turned out to be neurinomas [3451]. The most frequent site of these tumors is cervical, followed by thoracic.

There are also very rare reports of intramedullary neurinomas [2602, 2738, 3710, 2791, 2724, 3106, 1187, 2556, 3494, 2846, 1310]. The hypothesis is that they originate from small nerve bundles penetrating the cord in association with a perforating blood vessel [2791]. Neurinomatous proliferations have been found in different diseases of the spinal cord, both degenerative and traumatic, even associated with reactive gliosis. It has been hypothesized that, even though these proliferations have neoplastic features, they may represent a reactive process [2650, 2868, 142, 2824] which can be found even in the normal spinal cord [2501, 2964]. (For details on schwannosis in von Recklinghausen's disease, see Chap. 21). Neurinomas may affect the peripheral nerves at various locations.

### 17.1.3

#### Clinical Features

When the tumor affects the eighth cranial nerve, the main symptoms are hearing loss, tinnitus, and disequilibrium with vertigo. It is very important to accurately analyze hearing loss and vertigo, as this may be very helpful in diagnosing early stages of the tumor, when it is still in the acoustic canal. When the tumor reaches the cerebello-pontine angle, cranial nerve involvement, in particular of nerves VII, VI, and V, becomes evident. Late symptoms are increased intracranial pressure and cerebellar hemispheric syndrome.

Schwannomas of other cranial nerves show specific symptoms concerning the cranial nerves involved. In the spinal canal, the symptomatology includes radicular pain and a spinal compression syndrome.





**Fig. 17.3.** Neurinoma; the tumor is lobulated and cystic

#### 17.1.4

##### Macroscopic Appearance and Imaging

Neurinomas are usually solid, circumscribed, and encapsulated tumors, hard and elastic in consistency. Sometimes they are polylobulated, and the lobules may be cystic (Fig. 17.3). Consistency is reduced in tumors with marked regressive phenomena. On the cut surface they may be grayish-pink or whitish-yellow and translucent, or reddish, depending on the presence of various regressive phenomena, for example, hemorrhage.

First, plain tomographs of the internal auditory canal demonstrate its enlargement. By computed tomography (CT) scan, a tumor may be discovered still inside the meatus, but it frequently goes undetected. Outside the meatus it appears as a hypo- or isodense lesion with homogeneous enhancement. There are features which help in distinguishing a schwannoma from a meningioma; one is the flat attachment of the latter to the petrous bone. CT scan provides helpful information on the bony anatomy.

Magnetic resonance imaging (MRI) is the modality of choice, especially for intracanalicular tumors. Tumors can be seen on T1-weighted images and show enhancement after gadolinium. The tumors can be classified on the basis of CT and MRI into three groups: intracanalicular, medium-sized, and large. Very important for the diagnosis are audiometry, speech discrimination, caloric testing, auditory evoked brain stem response, electrocochleography, and electroneuronography. CT and MRI are useful also for schwannomas of other cranial nerves and for those of spinal roots.

### 17.1.5

#### Microscopic Appearance

Histologically, two main forms are distinguishable, A and B according to Antoni [75] or first and second according to Henschen [1295] and Jumentié [1562].

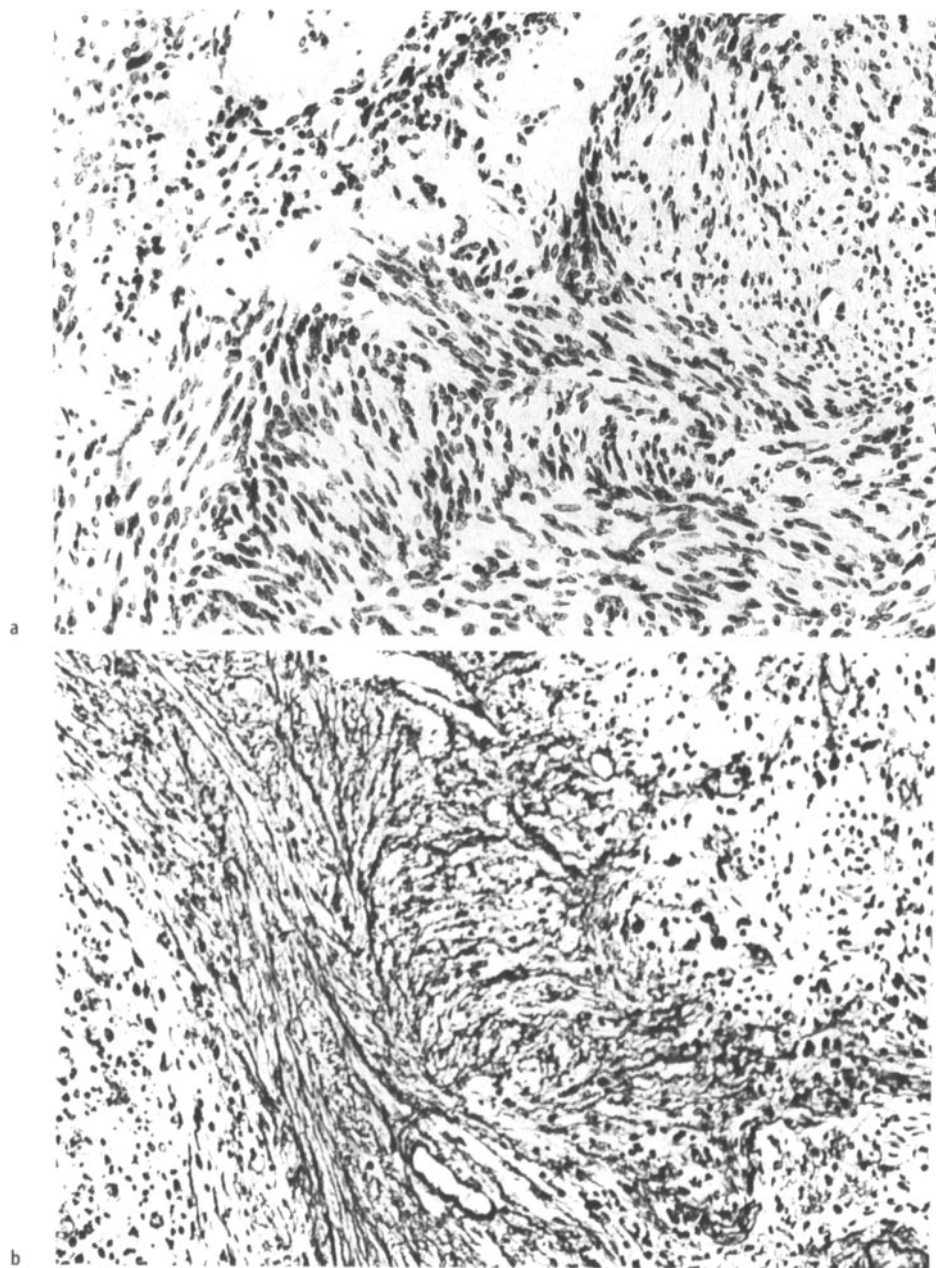
The A type is compact and fibrillary and is formed by elongated cells not easily distinguishable from each other. They are arranged in bundles with various orientations and in whorls (Fig. 17.4a). The nuclei are elongated and cigar-shaped and tend to align themselves at the same level in the bundles, forming “palisades” (Fig. 17.5a). In transverse section, they appear roundish. Sometimes nuclei are large and abnormal with inclusions, but this is not necessarily indicative of malignancy (Fig. 17.5b). Fine argentophilic fibers are arranged along the major axis of the cells (Fig. 17.4b), corresponding to basal membranes, and reticulin and collagen fibers radiate from the blood vessels or from the capsule.

The vascularity is variable, and the vessels are often cavernous and lined only by endothelium (Fig. 17.6a) or with thickened and hyalinized walls (Fig. 17.6b). Large lacunae without even an endothelial lining are sometimes found. Exceptional cases have been described with intratumoral or subarachnoid hemorrhage, related to the abundant vascularity and to the weakness of the vessel walls [1892]. This appearance could be a feature of larger tumors [1601].

In type B, the tissue is loose, vacuolated, and often cystic. The cells acquire an astrocyte-like appearance (Fig. 17.7a). Often fatty degeneration is found (Fig. 17.7b), which gives the cells a honeycomb appearance. Frequently, accumulations of intra- and extracellular pigment occur (Fig. 17.8). This can be due to hemosiderin or may be composed of lipopigments of ceroid type which could be produced by the Schwann cells themselves, recalling the capacity of these cells to produce myelin [2348]. The lipid constituents of neurinomas (phosphatides, cerebrosides, cholesterol, and cholesterol esters) are identical to those of the myelin sheath [1283, 2349]. The “fatty degeneration,” therefore, might not be a true degeneration but the result of a thesaurismotic activity [539]. The pattern of associated esterase enzymatic activities is similar to that of the white matter oligodendrocytes [2300, 3006]. Ganglion cells from the ganglion of Scarpa are not uncommonly found within the tumor.

Under the electron microscope, the variations in shape of the different cell types appear as a modulation of the same cell type [3624, 467, 590]. The constant features include the presence of a basement membrane surrounding the tumor cells and the interdigitation of cytoplasmic processes, with 200-Å gaps (Fig. 17.9). The fine argentophilic fibrils, much discussed during light microscopy study, correspond to the basement membrane seen with electron microscopy. The supporters of the neuroectodermal origin of the neoplasm emphasize that the presence of the basement membranes is a direct demonstration of the Schwann cell nature of the tumor cells. According to others [3584, 590], the perineural fibroblasts also have a basement membrane. However, the absence of a basement membrane could not exclude the derivation of the tumor from Schwann cells, because the primitive and immature lemmoblasts do not possess one.

The origin of the collagen in the tumor has been a matter of debate. According to some, it is the product of fibroblasts, but according to others its manufacture by Schwann cells cannot be excluded.



**Fig. 17.4a,b.** Neurinoma. **a** Cells are arranged in bundles. H&E,  $\times 200$ . **b** Densely packed reticulin fibers. Gomori,  $\times 200$

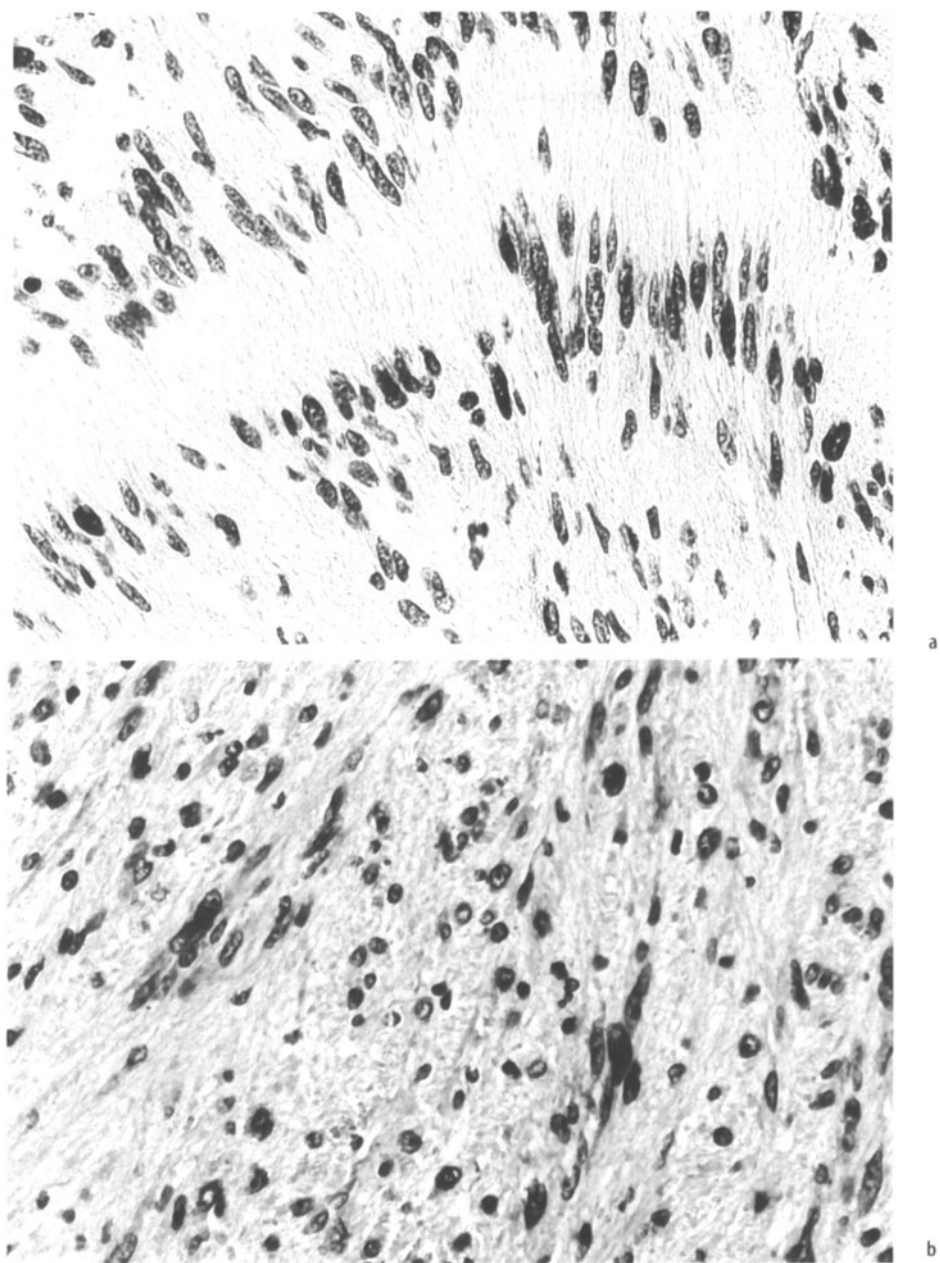


Fig. 17.5a,b. Neurinoma. a Typical palisades of nuclei. b Polymorphic nuclei. H&E,  $\times 400$

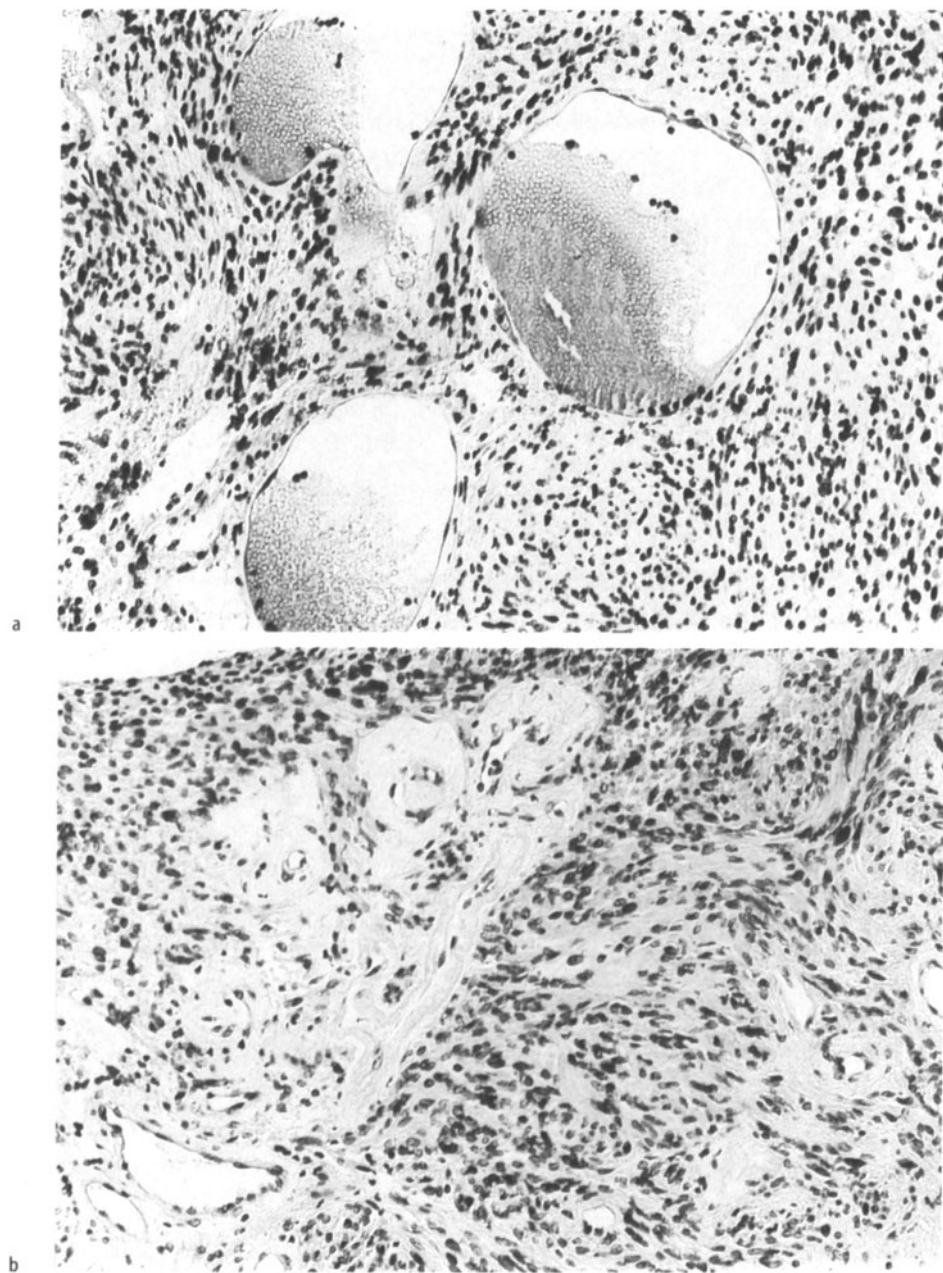
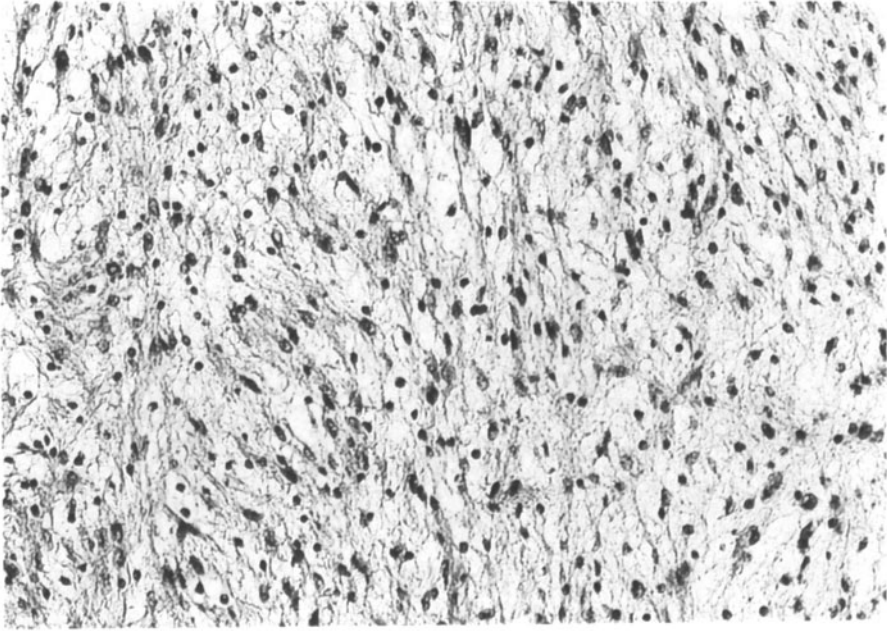
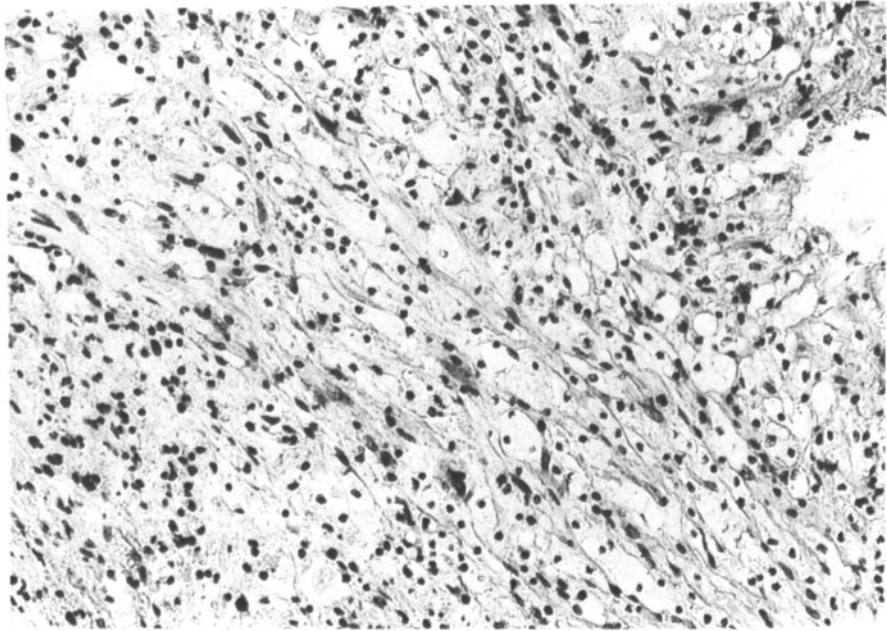


Fig. 17.6a,b. Neurinoma. a Vessels of cavernous type. b Hyaline degeneration of vessels. H&E,  $\times 200$



a



b

**Fig. 17.7a,b.** Neurinoma. **a** B area with typical loose aspect. H&E,  $\times 250$ . **b** Fatty degeneration. H&E,  $\times 200$

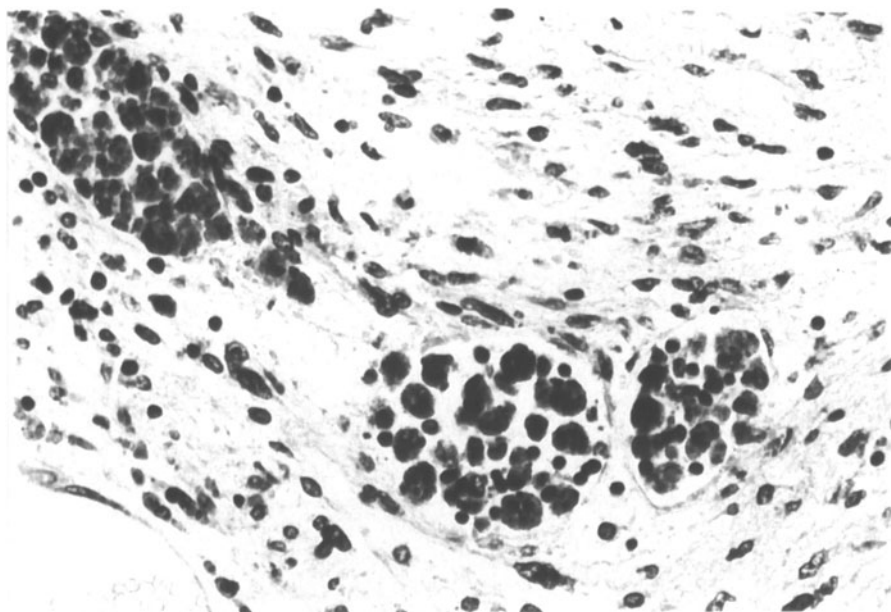


Fig. 17.8. Accumulation of pigment. H&E,  $\times 400$

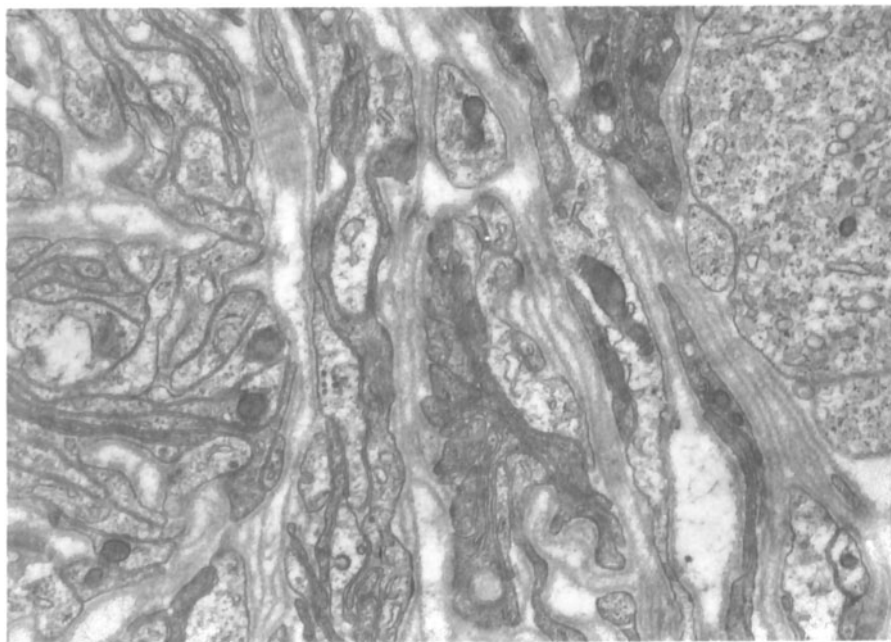


Fig. 17.9. Neurinoma, interdigitating processes of tumor cells surrounded by basement membrane.  $\times 18000$ . (From [2994])



Long-spaced collagen fibrils with 120- to 150-nm banding periodicity ("Luse bodies") [2048] are found in direct contact with the basement membranes [590]. Direct evidence of collagen production by Schwann cells is lacking, but it is thought that there is a process of organization of the collagen in which the glycosaminoglycan (GAG) of the basement membrane may play an important role [2292].

Immunohistochemically, two main antigens are in evidence, S-100 protein [3640] and Leu-7 (HNK-1) [2611], even though they cannot be considered as specific. Conversely, glial fibrillary acidic protein (GFAP) may be positive, both in the majority of neurinomas and in many neurofibromas [2234, 1143, 3285, 2086]. This finding is, however, controversial: In some experiments in which a monoclonal antibody was employed, no staining was observed [3464]. It is possible that in the heterogeneous group of GFAP polypeptides, those positive in Schwann cells are not identical to those positive in astrocytes [1540]. The laminin of the basement membrane is easily demonstrable immunohistochemically [2198].

Histologically, there are no major differences between unilateral vestibular schwannomas and those of neurofibromatosis-2 (NF-2); however, some differences have been found, e.g., more hyalinized and malformed vessels, recent and old thromboses, and hemosiderin deposits were found in unilateral vestibular tumor [3243].

Bilateral vestibular schwannomas of NF-2 appear more invasive, with a tendency to infiltrate the adjacent cranial nerves [1982]. A significant difference in the proliferation potential has been found between NF-2 and sporadic vestibular schwannomas, using MIB-1 and proliferating cell nuclear antigen (PCNA). The labeling indices (LI) were higher in NF-2 tumors [74].

### 17.1.6

#### Cellular Schwannoma

Within the category of cellular schwannoma, a variant has been delineated, characterized by high cellular density, mitotic figures, fascicular pattern, but without Verocay's bodies, and with a good prognosis [3719]. This variant is found mainly in peripheral nervous system (PNS), where it accounts for 10%, and is occasionally found intracranially or intraspinally [915, 2000]. In a recent series of 12 intracranial and intraspinal cases [714], the LI of PCNA was 44.6% compared to 8.1% in classical schwannomas.

This variant must not be confused with malignant PNS tumors (MPNST), which are less demarcated and show a higher number of mitoses, cell atypia, and necroses.

### 17.1.7

#### In Vitro Culture

The cells growing in culture are identical to those found in Antoni A and B areas [2364, 2363, 2045]. The former are elongated and bipolar and arranged in a tandem fashion, while the latter have an ameboid appearance, with processes arranged in a characteristic way. According to some investigators [1665, 2045], they may transform into *Gitterzellen*, demonstrating the capacity to phagocytose and to turn back



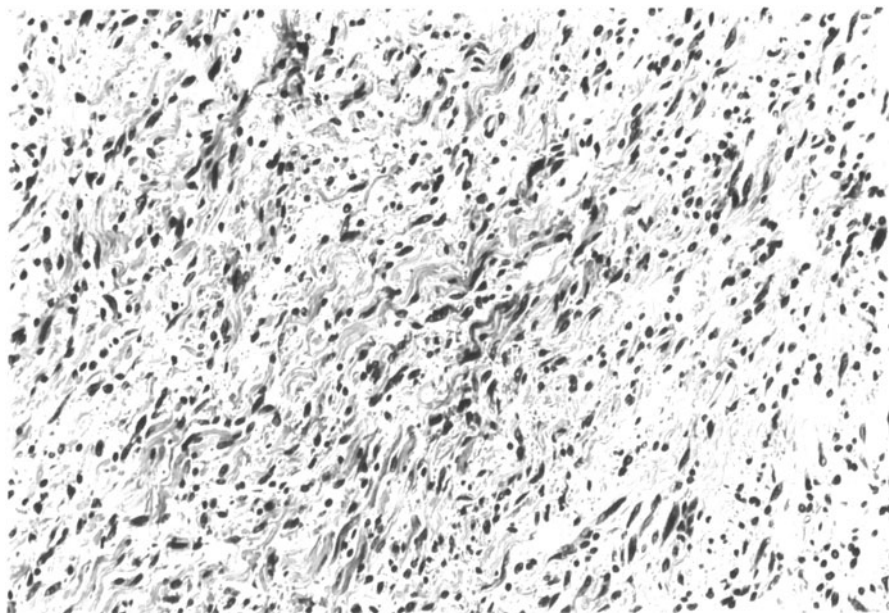


Fig. 17.10. Neurofibroma, elongated, twisted, and eel-shaped cells. H&E,  $\times 400$

into Schwann cells; however, this transformation has not been confirmed by others [592]. The origin of macrophages from Schwann cells has subsequently been observed [847]. The existence of a developed lysosomal apparatus in macrophages can be demonstrated by adding a fluorescent cationic dye to the medium. This may also be noted, to a lesser extent, in elongated type A Schwann cells [930].

Neurinomas have also been maintained in organotypic culture, in which the production of an abundant basement membrane in the extracellular spaces and long spacing collagen [557] have been observed, as already reported [592].

## 17.2

### Neurofibromas

Even though basically formed by Schwann cells, neurofibromas are rich in collagen fibers and connective fibers and quite often contain nerve fibers (Fig. 17.10). They usually develop in association with von Recklinghausen's disease, but are sometimes solitary, e.g., dermal neurofibroma.

Dermal or solitary neurofibroma is a well-circumscribed, nonencapsulated mass located in the dermis and subcutis. It grows, expanding the nerve. Histologically, the tumors are formed by elongated, fusiform cells, associated with collagen fibers and a mucoid matrix. Sometimes Schwann cells may set in whorls resembling Antoni A areas. They may show hyaline degeneration, lymphocyte infiltrates, and specific differentiation, such as Wagner–Meissner bodies [835]. In a case with symmetrical distribution of tumors, distribution of Schwann cells around nerve fibers in an onion-

bulb formation was described. A transition between onion bulbs and microneurinomas was present [3069]

A variant of neurofibroma contains specialized pressure receptors such as Pacinian corpuscles [2691]. It is very rare, is found in hands, feet, and buttocks, and is called Pacinian neurofibroma. Another rare variant is the epithelioid neurofibroma, which has Schwann cells disposed in cords or nests and shows an “epithelial” aspect, but is clearly positive for S-100 protein. A pigmented variant has also been described.

### 17.2.1

#### Plexiform Neurofibromas

Plexiform neurofibromas are usually multiple and associated with von Recklinghausen’s disease. They should be considered as an expression of this disease even when they are apparently solitary. The tumor affects cranial and spinal nerves, including sympathetic ganglia and plexuses. The main locations are the neck, the mediastinum, the retroperitoneum, and the limbs. The tumor enlarges the nerve, transforming it into a “bag of worms” [835]. When an entire extremity is involved, elephantiasis neuromatosa may develop.

Microscopically, expanded nerve branches appear in different plane sections, infiltrated by Schwann cells interspersed with thick wavy collagen bundles and a mucinous matrix, among which axons can be demonstrated. Polymorphic nuclei and mitotic figures are evident. Under the electron microscope, Schwann cells show a basal lamina, whereas fibroblasts do not. In the early stage, a simple increase in endoneural matrix material occurs. Lymphocyte infiltrates and foamy cells can be found, as well as differentiated structures such as Meissner corpuscles. The latter appear under electron microscopy as aligned arrays of basement membranes which have been interpreted as being either of perineural [3635], Schwann cell [1877], or mixed [3233] origin. Recently, particular attention has been devoted to perineural participation in plexiform neurofibroma [842], and S-100 protein-positive Schwann cells have been contrasted with to S-100-negative perineural cells; however, cells with a mixed character [1335] have been described, in line with the interpretation of perineural cells as simple functional variants of Schwann cells [557].

Plexiform neurofibroma has the propensity to become malignant, and the vast majority of malignant tumors are part of von Recklinghausen’s disease.

A variant called diffuse neurofibroma occurs in children and young adults and is located mainly in the head and neck regions. There is also a neuromuscular hamartoma – the so-called benign triton tumor – which is extremely rare and is formed by multinodular masses composed of differentiated skeletal muscle fibers in association with myelinated and nonmyelinated nerves.

## 17.3

### Granular Cell Tumors

Granular cell tumor appears as solitary or multiple nodules located in the dermis, subcutis, or submucosa of adults. The most common site is the tongue, followed by

the chest and upper limbs. These tumors are poorly circumscribed and composed of polygonal, plump cells containing periodic acid-Schiff (PAS)-positive granules which, under the electron microscope, correspond to dense bodies. The cells are positive for S-100 protein and may contain myelinated or nonmyelinated axons [493]. The histogenesis of these tumors is not well known. Because of their association with nerves and the occurrence of a basement membrane, they have been regarded as originating from Schwann cells [908]. Positivity for S-100 protein agrees with this derivation. Granular cell tumors are identical to those found in the CNS, especially in the neurohypophyseal region. Very rarely, these tumors may be malignant.

## 17.4

### Neurothekeoma

Neurothekeoma, also known as nerve sheath myxoma [1011], appears as a nodule in the skin of the head, neck, or shoulders in children or young adults. It is composed of lobules of cells of an astrocytic or epithelial appearance within a myxoid matrix, formed by GAG. The cells are positive for S-100 protein and negative for epithelial membrane antigen (EMA) and Leu-7, indicating that they are of Schwann cell and not perineural origin [400].

## 17.5

### Perineurioma

Perineurioma is a rare lesion affecting the extremities of young people, causing a motor mononeuropathy. It appears as a mass enlarging the nerve, even at a distance, histologically formed by onion-like structures, similar to those seen in hypertrophic neuropathy (see Fig. 17.13b). The cells, however, also diffuse into the endoneural compartment. They are negative for S-100 protein and positive for EMA [2904], and it remains to be established whether the lesion is a neoplasm or a reactive response.

## 17.6

### Prognosis, Malignancy

Not infrequently, large, haphazardly distributed or clustered cells with large and hyperchromatic nuclei are found. Their significance is uncertain, but they are not related to malignancy.

Neurinomas in general do not become malignant and do not metastasize. A malignant variety has been described in peripheral nerves, mostly in von Recklinghausen's disease, and exceptionally in the cranial nerves, mostly in tumors arising from the Gasserian ganglion or from branches of the fifth nerve. Of 19 patients with malignant Schwannoma, five had a primary spinal tumor [3495].

Malignant Schwannomas arise *de novo* and not from preexisting schwannomas, preferentially from peripheral nerves, in association with von Recklinghausen's disease. They recur repeatedly after the operation, show increasing malignancy, and are

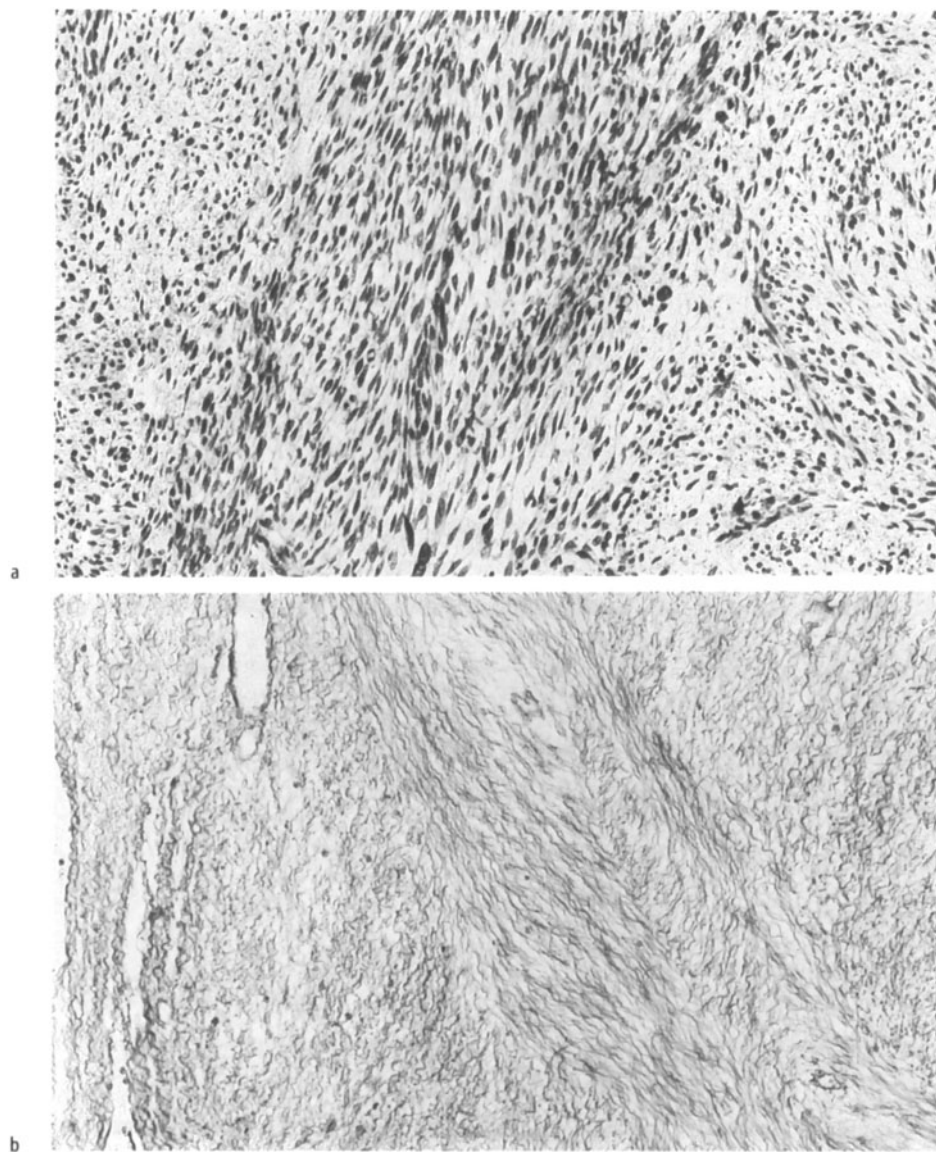
eventually indistinguishable from malignant neurofibromas of von Recklinghausen's disease. Previously called neurogenic sarcomas, they are included in the group of MPNST [774]. Intracranial solitary malignant schwannomas are extremely rare, mostly affecting the trigeminal ganglion or its branches.

The tumors affect adults between 20 and 50 years of age – younger when in association with von Recklinghausen's disease – and more commonly affect men. The nerves of the trunk, neck, and limbs are involved. The tumors appear as large or fusiform masses within a nerve or eccentric to it, sometimes well delimited. They are difficult to recognize when the nerve is not seen. Histologically, they resemble fibrosarcomas, being composed of spindle cells with wavy and elongated nuclei which appear oval on transverse section. The cells are organized in bundles, accompanied by long, thin reticulin fibers (Fig. 17.11a,b), alternating with loose or myxoid areas. The cells may also be short or may form whorls. Even nuclear palisadings may be focally formed. Mitoses are evident (Fig. 17.12). A storiform appearance is also common. The tumor may grow in a plexiform manner, but after recurrences it infiltrates adjacent structures, mitoses become more frequent, and necroses appear; very polymorphic cells are evident, and the production of reticulin fibers decreases. Positivity for S-100 protein is preserved, as is the finding of basement membrane on electron microscopy.

Plexiform neurofibromas show a propensity to become malignant, usually when associated with von Recklinghausen's disease. Metaplasia is a frequent phenomenon in MPNST, with transformation into osteoid, cartilage, adipose tissue, and striated muscle cells; different variants have also been described, although these are quite rare. In addition to a melanotic variant, an epithelioid variant (Fig. 17.13a) has been identified [2748]. The cells take on an epithelioid aspect and are arranged in nodules or in short cords separated by a connective tissue stroma. The differential diagnosis from a melanoma or carcinoma is very difficult, and association of the tumor with a nerve may be of great help. Positivity for S-100 protein, which, however, is not a constant phenomenon, and negativity for cytokeratin are also helpful.

Some MPNST contain glandular formations made by non ciliated cuboidal or columnar cells, sometimes producing mucin, probably of enteric type. The glands are circumscribed and lined by a keratin-positive epithelium [3718]. This variety affects major nerves and is usually associated with von Recklinghausen's disease. The general aspect is that of an MPNST. The prognosis for patients with MPNST is very poor. The median disease-free survival time has been found to be 11 months, with a median overall survival of 44 months. Prognosis is slightly better in patients with neurofibromatosis [3606]. Therapy consists of aggressive surgery and adjuvant radiotherapy.

The variety with rhabdomyoblastic differentiation, known as triton tumor, deserves special mention. The term triton tumor should be used for any neoplasm showing neural and skeletal differentiation, including neuromuscular hamartoma (benign triton tumor), such as ectomesenchymomas [1594]. The name originates from the belief that, in the triton salamander, normal nerve induces regeneration of muscles. In practice, the term malignant triton tumor is reserved for malignant schwannomas with rhabdomyoblastic differentiation. This tumor is also very rare and is associated with von Recklinghausen's disease. Histologically, the tumor is a malignant schwannoma with rhabdomyoblasts which can be positive for desmin and actin.



**Fig. 17.11a,b.** Malignant peripheral nervous system tumor (MPNST). **a** Bundles of elongated cells with many mitoses. H&E,  $\times 200$ . **b** Preservation of reticulin fibers. Gomori,  $\times 200$

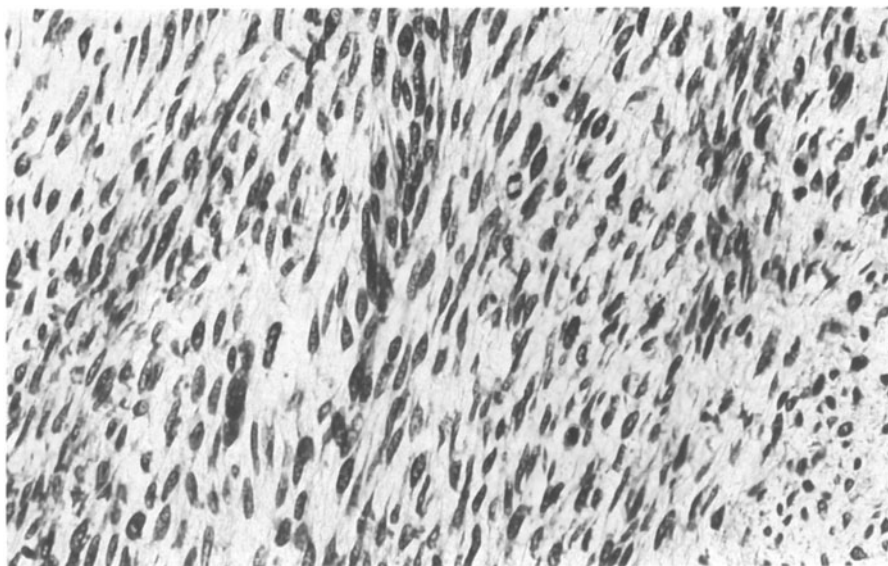


Fig. 17.12. Malignant peripheral nervous system tumor (MPNST), mitotic figures (higher-power magnification of Fig. 17.11a). H&E,  $\times 400$

MPNST recur frequently after operation and have a worse prognosis when associated with von Recklinghausen's disease, with metastases occurring within 2 years, mainly in lung, liver, subcutaneous tissue, and bone. Patients with solitary MPNST have a longer survival time.

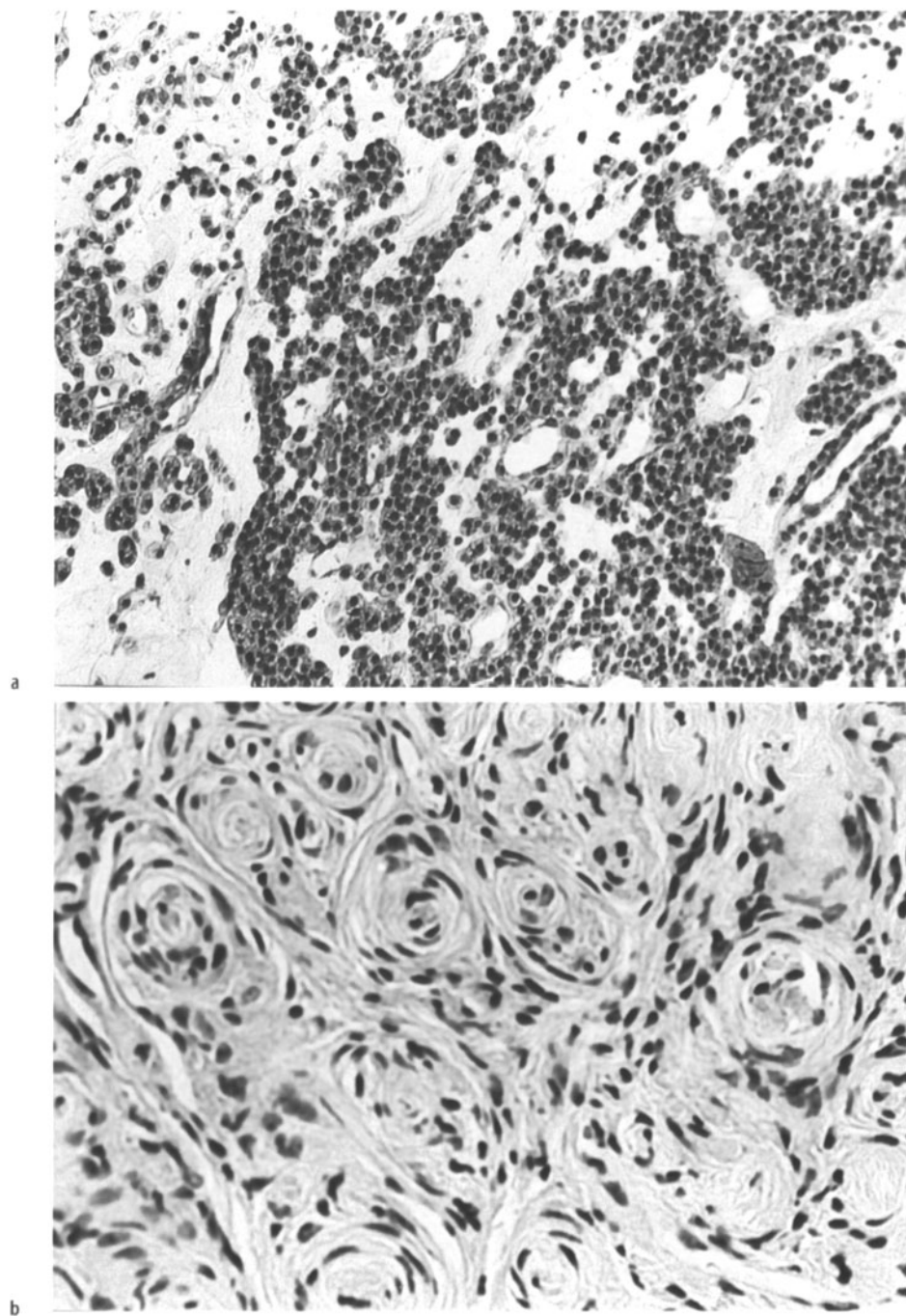


Fig. 17.13. a Malignant peripheral nervous system tumor (MPNST), epithelioid variant, H&E,  $\times 200$ . b Perineurioma, onion-bulb formations, H&E,  $\times 200$ . (From [2994a])

## Tumors of the Meninges

### 18.1

#### Meningiomas

##### 18.1.1

##### General Considerations and Nomenclature

The first accounts of meningeal tumors were those of Louis [2023] and Cruveilhier [610], while the first distinction of “psammomas” from fibromas and dural sarcomas was made by Virchow [3556]. However, it was with Bailey [128] and Cushing [623, 626] that the nosography of meningiomas was outlined, as for many other tumors of the CNS. It is evident that both the terminology and the various classifications proposed reflected all the uncertainties regarding the tissue of origin of meningiomas [2974]. For many years, for example, the opinion that these tumors originated from endothelial “dural” cells prevailed, so that they were called “dural endotheliomas.” Cleland [530] commented on their possible origin from arachnoid cells which had remained included in the dura, an idea which was reaffirmed and sustained by Schmidt [3057] and by Cushing and Weed [630]. Though the origin of endotheliomatous meningioma from arachnoid residues in the zones of development of pacchionian granulations is today generally accepted, uncertainties still exist for the fibroblastic type [3708]. Many have attempted to clarify the last point. Mallory [2083] and Penfield [2603], on the basis of Ribbert’s concept [2775], tried to demonstrate that the fibroblast is the typical cell composing a meningioma. They proposed the term “fibroblastoma.” On the other hand, other authors [2468, 2860, 2859], and in general the French school, sustained the neuroectodermal origin of the leptomeninges and of the neoplastic derivatives. Faced with these contrasting opinions, grounded mainly on embryogenetic criteria, classifications based on morphological and biological criteria became increasingly important.

The use of embryogenetic criteria appeared, however, to be very complicated [1099]. The possible origin of the tumors from embryonal remains, which were responsible for their growth, became the basis for interpreting the presence of various cellular forms within the confines of the ontogenetic differentiation, e.g., fibroblasts, angioblasts, osteoblasts. It was somewhat more difficult to ascertain whether all the structural elements of the tumor, such as the blood vessels and fibers, derived from the meningotheial cells of the arachnoid. However, in the light of phylogenetic and ontogenetic considerations, it seemed reasonable to concede that one or more components of the various layers of the meninges (and therefore of the diverse structures of meningeal tumors) could originate from embryonal residues and then differenti-



ate. The frequent presence of remnants of poorly differentiated meningeal tissue in some cerebral malformations supported this interpretation.

The term meningioma was coined by Cushing [623], who adopted it to avoid futile discussions on histogenesis. According to the concept of Cushing and Eisenhardt [629], in meningiomas there is a basic cell which could appear sometimes in a pure form and sometimes in a variously modified form thereby justifying the variants.

Because of uncertainties regarding the classification and nomenclature (fibroblastoma or endothelioma), which reflected the histological composition of the meninges, i.e., meningothelial cells and fibroblasts, the introduction of the term meningioma was expedient to end the debate. Moreover, it corresponded to the anatomical situation.

The dura mater is formed by connective tissue with parallel and interwoven fibers, fibroblasts, and large cells within the interstices. The arachnoid is formed by fibrils interwoven with fibroblasts, lymphocytes, and histiocytes. It has an external thin layer containing epithelial-like cells with a covering function called meningothelial cells. Under the electron microscope, the meningothelial cells show an extreme interdigitation of the cell membranes [1636] which cannot be recognized by light microscopy and the cell membranes appear so fuzzy as to give rise to the syncytial appearance. Meningothelial cells are not only in direct contact with the inner dural layer formed by the so-called cells of the dural border without any real interposed space, but the two layers even merge, also forming serrate junctions with desmosomes [2967]. A thin basal lamina then separates the external arachnoid layer from the inner one [1642]. It has to be taken into account that in culture, meningothelial cells form whorls [1666] and that in normal arachnoid villi, these undergo calcification. There is, in general, agreement that meningiomas arise from the arachnoid, in particular from its external layer, but other cellular components of the arachnoid, for example fibroblasts, which are found in the inner layer, may contribute to their composition: This could explain the frequent biphasic, meningothelial and fibroblastic, appearance [1642].

An unresolved problem which has influenced the classification of meningiomas is that of the embryology of the meninges. Even if there is general agreement that the primitive meninx derives from the condensation of the mesenchymal layer situated around the neural tube, between this and the ectoderm, discussions regarding the participation of the neural crest in its formation are still going on. One should not forget that all the variants of meningioma (e.g., chondro-, fibro-, angioblastic) follow the lines of mesenchymal differentiation, while there is no aspect categorically supporting derivation from the neural crest: There are no doubts that meningioma must be considered a mesodermic tumor [2871, 1642].

If an all-embracing classification, including clinical and neuroimaging characteristics, must be adopted, the 1979 WHO classification is not completely satisfying. Such a need does exist [1523], so the suggestion to renounce the desperate search for the cells of origin and to follow that of identifying specific cell differentiations [2976] seems most promising.

In this book the classification scheme recently proposed by the WHO is adopted.

### 18.1.2

#### Frequency

In the series of 2023 primitive intracranial tumors of Cushing [627], meningiomas represent 13.4%. In various North American neurosurgical series, they vary from 13% to 19% [1642]. In pathological series, they represent 17%–18% [3799, 2994, 3803]. In our present pathological and surgical collection of 8549 cases, they represent 18%.

It is to be noted that in neurosurgical series, meningiomas found casually at autopsy are not considered. On the other hand, asymptomatic meningiomas may be found by computed tomography (CT) scan; they do not necessarily grow further [904]. Therefore, the average incidence of some series can be calculated to be about 20%.

The geographic distribution is fairly uniform throughout the world, with the exception of Africa, where meningiomas seem to be more frequent. This, however, may be a relative factor, more expressive of a lower incidence of gliomas [974].

Regarding populations, the Rochester studies give an incidence of 6/100 000 in a clinical and postmortem series [1824], while another clinical series gives 2.3/100 000 [2819], similar to that in the reports before CT came into use.

### 18.1.3

#### Age

Meningiomas are single or multiple tumors clearly more common in adults. In large series, the average age found varies from 46 [627] to 45 years [3799]. In a personal series, there is a clear-cut preponderance in the sixth decade of life, with an average age of 51 years. It has to be underlined that the frequencies according to age differ between surgical and autopsy series; of 300 asymptomatic tumors found at autopsy, 100 were meningiomas, and these occurred more frequently in the seventh and eighth decades. By contrast, symptomatic cases were concentrated in the fifth decade [3716].

Meningiomas are rare in infancy: The percentage varies from 1.1% to 4% [3393, 629, 618, 607, 1314, 2947, 657, 761]. To date, 197 cases have been reported in the literature [888]. In the personal series of pediatric intracranial tumors, they represent 1.4%. In 15%–20% of cases, the tumors are intraventricular [759]. There are rare reports of congenital meningiomas [2237, 379].

Some observations indicate a more malignant character of meningiomas in childhood [607], probably because of the prevalence of the hemangiopericytic and papillary variants [2903], a higher incidence of intraventricular [2462] and spinal epidural meningiomas [423], and a male rather than a female preponderance [2339]. Exceptional cases of giant tumors situated in the parieto-occipital region [2154] and in the foramen magnum [3207] have been reported. In a recent review of 23 patients, the absence of the female predominance was confirmed. Location and histology were similar to those in adults [1048].

Meningiomas tend to occur more frequently in patients over the age of 60 years: 35% in the series of Cooney and Solitare [561]. With advanced age, the higher percentage may be expressive of the high frequency of “incidental” meningiomas, i.e., which do not cause death and are occasional autopsy findings.

#### 18.1.4

##### Sex

The prevalence for the female sex is unanimously acknowledged [3799, 1642, 2904]. In the personal series, the female to male ratio is 1.8:1. It has to be noted that the difference between the sexes disappears, as has in part been said, above and below a certain age [1642]. The preponderance of the female sex in middle age is due to estrogen stimulation, generally recognized as a growth factor for tumors. The same explanation is given for the rapid growth of meningiomas in pregnancy, especially those close to the sella turcica. Whether it is real growth or a reversible increase in volume caused by electrolytic imbalance has yet to be established with certainty [2255]. Another factor suggesting the importance of female hormones in the growth of meningiomas is given by the more than casual association between these tumors and breast carcinoma [3076]. This is one of the arguments for considering meningioma as a hormone-dependent tumor. In fact, estrogen and progesterone receptors have been found in a certain number of cases, both biochemically and histologically [751, 2656, 3064, 3439, 3763, 1323, 2137].

The evidence for the association between meningioma and breast carcinoma rests on 36 reported cases in the literature [1723]. In six women, not only was the breast carcinoma associated with meningioma of the sphenoid ridge, but a genital tumor was also present [1486]. It has been proposed that a disturbance of the regulation of the oncogenes, similar for the two tumors, is the basis of this association. The possibility that in a breast cancer bearer neurological symptoms may be related to a meningioma and not to metastases has been emphasized [1723]. It is surprising that the large series of meningiomas reported by Cushing and Eisenhardt in 1938 and Zülch in 1956 have not included such observations.

#### 18.1.5

##### Familial Tendency

Meningiomas in members of the same family are found in NF-2 and also in the absence of this genetic affliction [1008, 3586, 1559, 1180, 3112].

#### 18.1.6

##### Trauma and Irradiation

Trauma does not seem to play a real role in the pathogenesis of meningiomas. There is no definite evidence for the proposed viral etiology. In contrast, irradiation has been shown to be important.

The development of meningiomas after irradiation is a well-established fact. The first incontrovertible demonstrations were the observations of meningiomas arising after irradiation for tinea capitis in children [2290, 3245]. The mean latency period between the time of irradiation and the clinical presentation was approximately 36–38 years [2865]. For the biological and clinical characteristics, radiation-induced meningiomas were defined as a separate nosological subgroup. Histologically, these tu-

mors show high cellularity, pleomorphism, and giant cells. Biologically, they show a higher multiplicity and a higher recurrence rate than those of nonirradiated patients [2865]. The number of observed cases was quite high: 42 [3245] and 41 [2865].

Two major subgroups of radiation-induced meningiomas have usually been defined: after low-dose irradiation and high-dose irradiation. An example of the first modality is irradiation for tinea capitis, and of the second modality is irradiation for tumors (2000–9000 cGy). Twenty-seven cases of meningiomas after high-dose irradiation are reported in a review [2932] from which it emerges that the brain-irradiated brain tumors were of different types.

Two cases in which meningioma developed after irradiation for acute lymphocytic leukemia have recently been presented [898], in line with the observation that the risk of developing nervous system tumors, including meningiomas, is tremendously increased in children with acute lymphocytic leukemia treated by chemo- and radiotherapy [2400]. In one of these patients, there was a “cryptic” vascular malformation, as in most cases of another series [2061].

In children, 15 cases have been reported (personal cases and from the literature) [1062]. They are mostly calvarial, benign, rarely multiple, and with a latency period shorter than those arising after low-dose irradiation. The problem of the specific location of radiation-induced meningiomas has been discussed, because it seems that the location is due to the technique of irradiation. The localization to the calvarium is typical after irradiation according to Adamson-Kienböck for tinea capitis. After full-mouth dental X-ray studies, the site at risk is the skull base [2683].

There is an inverse relationship between dose and age and time to tumor formation. The higher the dose, the shorter the latency period; the lower the age, the shorter the latency period [2061]. However, the latency period is usually long, even though cases with a very short period after high-dose irradiation have been reported [2907].

### 18.1.7

#### Association with Other Tumors

Even excluding neurofibromatosis, an association with other tumors is frequent, mostly with gliomas and in particular glioblastomas. Several cases have been reported [2100, 2994, 1642, 939]. It may be merely a coincidental association, given the frequency of these tumors, but there may also be a relationship dependent upon the effect of the stimulus of one tumor on the other [2377], especially if the meningioma is malignant. An association with pituitary adenomas, intestinal carcinoids, parathyroid adenomas, and choroid plexus melanoma has also been reported [1642]. Among nontumoral lesions, aneurysms are those most frequently associated with meningiomas [939]. In exceptional instances, carcinomatous metastases in a meningioma have been described [884, 224]. In this context, it should be remembered that carcinomatous metastases to the meninges are not infrequent [208, 360, 651, 2109, 3283].

### 18.1.8

#### Site

Intracranial meningiomas are more frequent than spinal ones, with a 16:1 ratio [627]. Four main sites are usually considered: intracranial, spinal, ventricular, and extracranial. At these sites meningiomas demonstrate elective locations which are statistically and embryologically significant.

In the intracranial region, the following elective sites are distinguished in order of frequency: parasagittal, convexity, sphenoid, Sylvian, olfactory groove, tuberculum sellae, parasellar, tentorium, Meckel's cave, falx, pontocerebellar angle, ventricles, clivus [626, 3799].

Parasagittal meningiomas are usually situated, in order of frequency, in the middle third of the sagittal sinus, the posterior third, and then the anterior third [2493, 1361, 3799]. The high incidence of meningiomas at these sites has been related to the frequent presence of pacchionian granulations, the importance of which has already been mentioned. Meningiomas often occupy the angle between the dura and the sinus, to which they are strongly adherent. Their development is mostly extracerebral, but sometimes they partially or totally penetrate the parenchyma, compressing and shifting it.

Convexity meningiomas are mostly located anteriorly; they do not show any relationship with the sinus but adhere to the dura mater, sometimes so tenaciously that it is impossible to dissect them away from it. This is the most common site for multiple meningiomas, which take on the appearance of multiple nodules of various sizes in the dura mater.

Sphenoidal meningiomas and those of the Sylvian region very often show similar modes of development. They are variable in shape, size, and direction of growth, and they may reach and occupy the middle or anterior fossa, or both. Sphenoid meningiomas have been further subdivided into those of the clinoid and those of the middle part of the sphenoidal angle. The global ones, involving the pterion, often have an "en plaque" appearance. A more recent categorization, more expressive of surgical considerations, is the petroclival category, which may involve the cavernous sinus and extend to the anterior clinoid process. Blood vessels and nerves of the base of the skull may become enveloped in the neoplastic mass which also sends tumor prongs into the neural parenchyma.

In the olfactory groove, the frontobasal structures, particularly the olfactory bulb, the optic nerve and the anterior cerebral arteries are affected. The tumor extends mostly towards the chiasm and the frontal lobes, often on both sides of the falx. Tumors arising from the optic nerve sheath have occasionally been reported [528].

As above, meningiomas of the tuberculum sellae and of the parasellar region (Fig. 18.1) particularly involve the chiasm, but also the optic and sometimes the olfactory nerves. They are usually small tumors which find their growth space in the frontobasal regions.

Tentorial meningiomas which arise from and adhere to this structure may develop in both the supra- and infratentorial regions. In the latter case, they take on the known dumbbell shape.

In Meckel's cave, they originate from the dural covering of the cavum itself and always develop in relation to the temporal lobe. Also, in this location they may present



Fig. 18.1. Multiple parasellar meningiomas

as “en plaque” growths or extend neoplastic prongs into the surrounding neural tissue. They are not common: overall, a total of 46 cases have been described up to and including 1983, plus two personal ones [406].

Meningiomas of the falx are to be distinguished from parasagittal meningiomas because, unlike the latter, they do not show a direct relationship with the superior sagittal sinus. Rather, they are adherent to the falx itself. They almost always develop towards the cerebral tissue, sometimes on both sides of the falx.

In the ponto-cerebellar angle, they follow, in general, the same modes of growth and involvement of the local structures of this region as other neoplasias.

The lateral ventricles are not infrequently involved [102, 1035]. These tumors adhere to the choroid plexuses, sometimes reaching sizable proportions, especially on the left (Fig. 18.2). Of 407 meningiomas reported in a series from 1958 [3473], eight were intraventricular. Seven of these were of the fibroblastic variety. The fourth ventricle is certainly one of the rarest sites: up to 1950, only two cases had been described [3559] and eight up to 1963 [471]. To date, ten cases have been reported, plus a recent one of the osteoblastic type [1546]. They may originate from the choroid plexus, most probably from the inferior tela choroidea [2971].

The clivus is one of the less frequent localizations. Because the tumors often develop in the direction of the foramen magnum and can reach the spinal canal, they are called craniospinal meningiomas. Many authors distinguish these tumors from those arising from below, which are called spinocranial meningiomas [3298].

Tumors may rarely originate from the intracranial part of the jugular foramen and extend extracranially or may, even more rarely, arise from the foramen itself [1462].

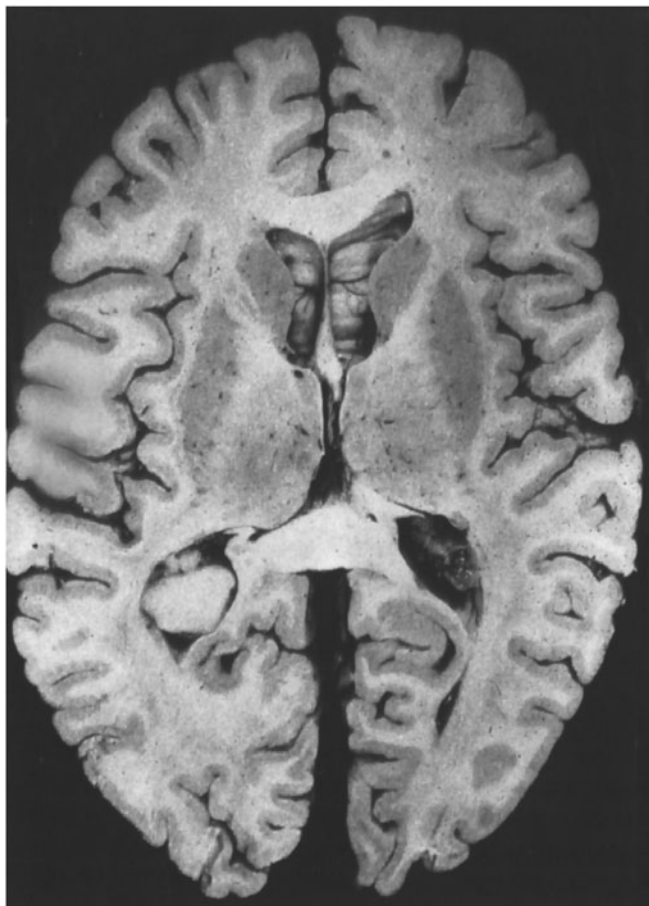


Fig. 18.2. Meningioma of the lateral ventricle

In general, meningiomas of the posterior fossa are not common. They represent 9% of 1854 cases collected from the literature [4]; the percentage varies in different series: 13.4% [629], 8.4% [451], and 4.2% (present series), with respect to intracranial meningiomas.

In relation to dural attachment, meningiomas are divided into those of the cerebellar convexity, tentorium, posterior surface of the temporal bone, clivus, and foramen magnum. Meningiomas formed 12.6% of 455 operated tumors of the posterior fossa [1891]. This percentage is not very far from that of meningiomas in general, with respect to the total of intracranial tumors.

Spinal meningiomas are far less frequent than intracranial ones: the ratio has been calculated to be 1:16 [627], but the relative percentage is quite variable, from 12.7% [3257] to 8.4% (personal series). The thoracic location is the most frequent. The relative frequency of meningiomas among primary spinal tumors, evaluated in many series, varies from 5.5% to 37.5% [2539].

Unusual extracranial and extraspinal sites are also found. This may be due to meningiomas extending from the cranial cavity, losing their site of origin. They may also be truly ectopic tumors, originating from arachnoid remnants, from arachnoid cells covering the craniospinal nerves at their point of exit, or they may even arise through metaplasia. Some have even hypothesized that they may arise without relationship to structures in the cranial and spinal cavities [1419].

The real frequency of extracranial meningiomas is not exactly known. Up to now, 504 cases have been reported with the same distribution for age and sex of intracranial tumors [3180]. The most common sites are the orbit, nasal cavities, paranasal sinuses, scalp, calvarium, orbit, and the region of the basal foramina. The tumors of the orbit represent the majority. They arise mostly from the meningeal sheath of the intraorbital portion of the optic nerve [3722]. Those of the calvarium may be intraosseous, calvarial, extracalvarial, or subgaleal [260, 2485]. Other sites include the oral cavity, parotid gland, ear, neck, mediastinum, and skin. Those in the skin have been distinguished in tumors of the scalp and paravertebral areas (mostly benign and found in infancy), tumors of the skin around the sensory organs (eye and ear), and tumors which grow in the skin but originate in the craniospinal cavity [2008]. Histologically, extracranial meningiomas are similar to the intracranial ones; very few are malignant. Their origin is a matter of debate. It seems possible that they derive from meningocytic cellular rests or from Schwann cells [3180].

### 18.1.9

#### Multiple Meningiomas

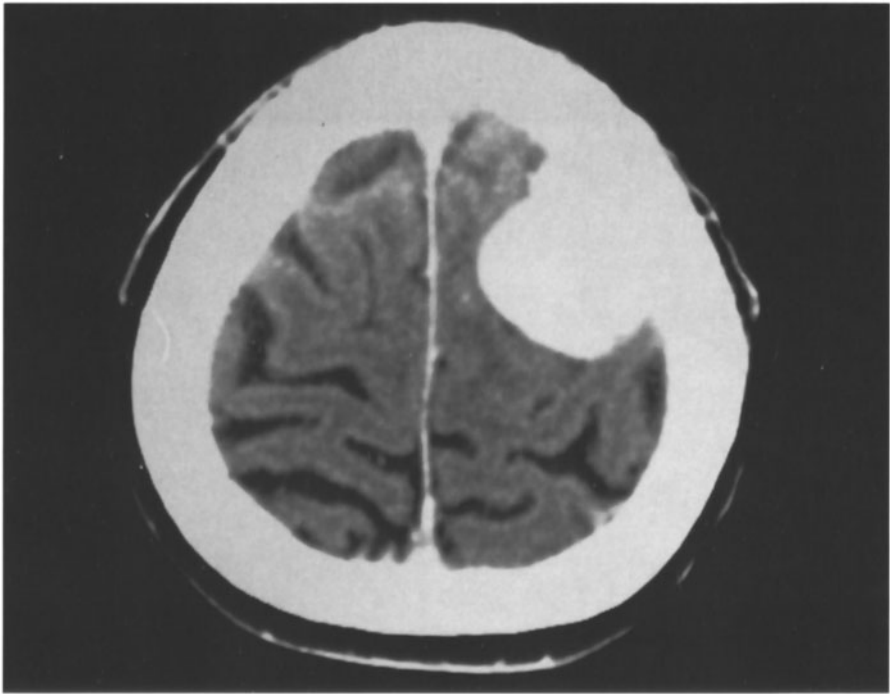
Multiple meningiomas frequently occur in neurofibromatosis NF2, but also independently of this condition. This entity has poorly defined nosographic limits with regard to meningiomatosis; if the meningiomas are numerous, the distinction from meningiomatosis is very difficult [2540, 3321, 296]. Meningiomas are not only multiple concurrently but also at different sites, and this must not be confused with recurrence. The incidence of multiple meningiomas varies from 1% to 2%–4% [2383, 1642, 815, 2557]. If, however, not only histological but also CT data are considered, the percentage rises to 4.4% [1997], 5.4%, or even 10.5% [2051, 2383, 869, 407]. In autopsy series, the frequency may reach 16% [3716], because asymptomatic tumors and elderly patients are included. Critical, comparative, clinical evaluation seems to indicate a proportion of 0.58% before and 4.5% after the introduction of CT scanning [748]. The occurrence of multiple meningiomas in the spinal canal is a rare event, but both supratentorial and spinal cases have been reported [576, 3780, 2426, 15, 1582].

### 18.1.10

#### Clinical Features and Imaging

There are no clinical signs or symptoms specific for meningiomas. When they are located in specific sites, typical clinical presentations for each site occur. Meningiomas may also grow asymptotically. Examination of large collections demonstrated that headache and paresis are common symptoms [2819].





a



b

As far as imaging is concerned, the method of choice is CT scan. The tumors are isodense or slightly hyperdense homogeneously unless calcifications are present. After contrast, there is an intense and homogeneous enhancement, with clear-cut demarcation of the border (Fig. 18.3a). Many tumors, however, show an atypical appearance, because of hypo- or hyperdense areas and nonhomogeneous enhancement. The picture may be due to regressive events, such as necroses [1878] or cystic degeneration, but also to edema. Focal necroses may appear as low-density areas, and if the tumor is completely necrotized, it may appear as an enhanced ring [1878]. Angiography is less important than it used to be. It is useful to visualize small communicating branches, especially from external carotid artery, and for the preoperative embolization. The tumor in the venous phase may be visualized through a uniform blush [1487]. On magnetic resonance imaging (MRI), the tumors appear mostly isointense on T1-weighted images; a minority is hypointense. On T2-weighted images, they may be either hyperintense or isointense. MRI can also be useful in recognizing the type of meningioma and edema, especially on T2-weighted images. After gadolinium most meningiomas, both intracranial and spinal, enhance intensely and homogeneously (Fig. 18.3b) [107]. Of particular importance is the possibility of seeing the enhanced dura next to the tumor borders, the so-called dura-tail, which is of great surgical relevance (Fig. 18.3b). Major advantages are now provided by MR spectroscopy, either hydrogen (proton) or phosphorus-based. A reduction in *N*-acetylaspartate and phosphocreatin/creatin peaks is typical for meningiomas.

A challenging problem is the distinction on CT or MRI between benign and malignant tumors. From the literature it seems that this is possible, and one of the most important signs might be the absence of visible calcifications. Another positive sign has been identified in mushrooming, but this is not universally accepted [3761]. Two other features relating to neuroimaging of meningiomas are similarly debated as possible indicators of malignancy: contrast enhancement and peritumoral edema. As to the first, there is no identifiable pattern of heterogeneity/homogeneity that could serve this purpose.

Like other tumors of the CNS, meningiomas induce peritumoral edema. This happens in 46%–92% of tumors [322, 1105]. Among the many possible factors responsible, four have been identified: disruption of the blood–brain barrier (BBB), mechanical compression, vascular compression, secretion of edematogenic factors or a combination of these [1969]. Many observations suggest that edema is associated with malignancy [2819], but there is no general agreement. Osteolysis has also been mentioned as related to aggressiveness of meningioma, but the association has not been confirmed. Positron emission tomography (PET) studies using F<sub>2</sub>-fluorodeoxyglucose provide useful information [677].

◁ Fig. 18.3. a Typical aspect on computed tomography (CT) of a convexity meningioma. b MRI: Intense gadolinium enhancement of a tentorial meningioma; the “dura tail” is evident

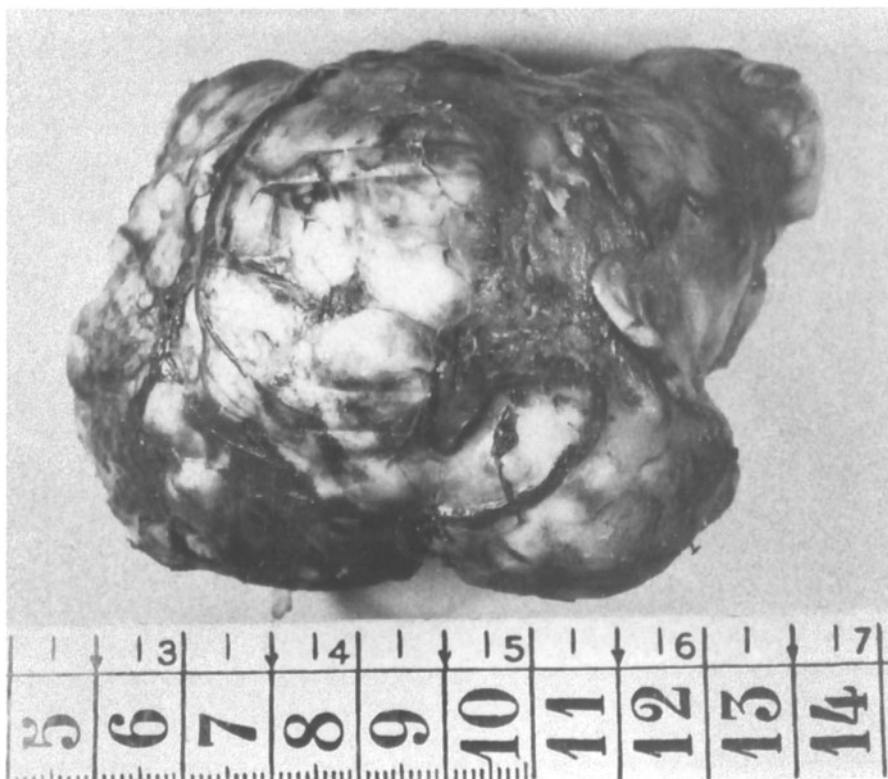


Fig. 18.4. Meningioma, hard and polylobulated mass

### 18.1.11

#### Macroscopic Appearance

In general, from the surgical point of view, meningiomas are distinguished into three types: the “iceberg” tumor (Fig. 18.4), so called because it is attached to the dura but embedded in the neural parenchyma; the “en plaque” type, which grows within the meninges and is most frequently situated on the sphenoid wing; and the type accompanied by bony hyperplasia, which is often located in the parasagittal region.

The tumor is usually well encapsulated and shiny with a smooth surface, reddish in colour, and has a hard-elastic consistency. On the cut surface, it appears mostly compact and fibrous. Many variations on these appearances, in part dependent on the histological type but often conditioned by regressive events, may be seen. For example, when fatty degeneration is present, the appearance of part or all of the tumor may be granular, yellowish, and of a soft, friable consistency. Calcification, which is rather frequent, may modify the color and especially the consistency of the tumor in the opposite way and may be felt on cutting. When meningiomas are multiple, especially over the convexity, they present as nodules more or less tenaciously adherent to the dura. Sometimes, the neoplastic masses, dura, eroded and/or hyperplastic cra-

nium are so compacted that they need to be removed en masse. When they are single, meningiomas have very variable dimensions, from the size of a pea to that of a large orange, or bigger. The weight of the fresh tumor varies from a few to several grams. In two cases reported by Zülch [3799], it was 835 g and 1300 g, including the infiltrated bone in the latter. The largest specimen of the personal series reached 550 g. The shape also shows marked variations, especially in relation to the location of the tumor. It may be roundish, elongated, “en plaque,” dumb-bell, etc.

In the majority of cases, meningiomas create a space by compressing the surrounding neural tissue, forming niches in the neural parenchyma or growing in pre-existing spaces such as the ventricles and the subarachnoid cisterns. The growth tends to follow pathways of lesser resistance. The tumors demonstrate an altogether different behavior with respect to mesodermal structures, such as the falx, tentorium, dura, and bone. In fact, these are infiltrated by the neoplastic proliferation, even if they are certainly benign, both histologically and biologically.

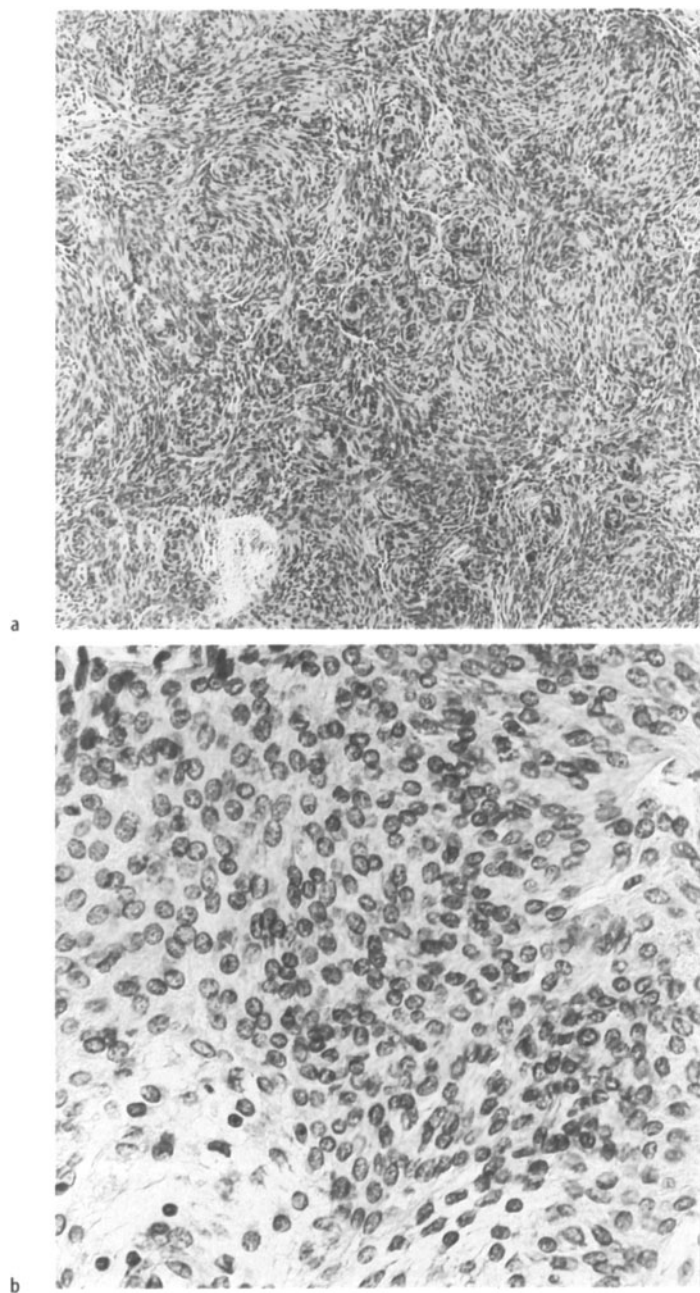
Meningiomas of the base of the skull, those of the sphenoid, and of the Sylvian fissure take on an “en plaque” appearance more frequently than others, engulfing and constricting nearby vascular and neural structures because of the way they grow along the meningeal planes. Both erosive and hyperplastic bony changes are often associated with meningiomas, especially in the parasagittal, convexity, and sphenoidal locations. Sphenoid tumors cause changes in the sella, such as decalcification and erosion, more frequently than those of the sellar region. Spinal meningiomas, as the intracranial ones, adhere densely to the dura. They are mostly situated in the subdural space, in a lateral position and in direct relationship with the spinal roots, and may take on different shapes and sizes, but are generally rounded or elongated. Even at this site, they may present as multiple tumor nodules. The presence of intratumoral cysts is fairly rare.

### 18.1.12

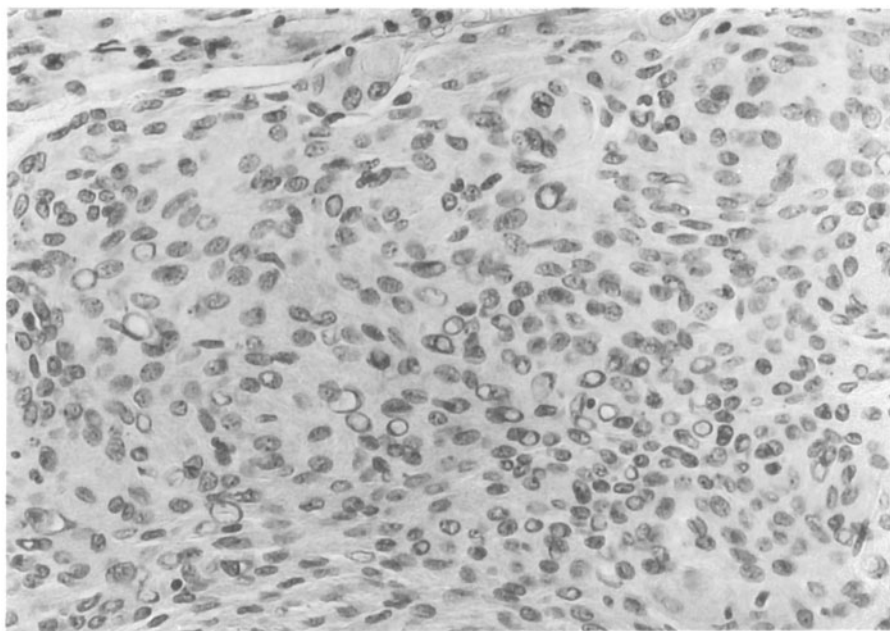
#### Microscopic Appearance

Meningiomas usually show a high cell density and are composed of polygonal, rather large, epithelial-like cells arranged in lobules, trellises, or islands, with a syncytial appearance (Fig. 18.5a). Parenchymal cells in the common histological preparations demonstrate ill-defined borders (Fig. 18.5b). The discretely eosinophilic cytoplasm usually appears homogeneous and is sometimes finely granular. The nuclei, of average size, rounded or slightly elongated, have a discrete quantity of mostly uniformly stippled chromatin, sometimes clustered on the nuclear membrane, and show the presence of one to two nucleoli. In some areas of the tumor, with marked variations from one case to the other, the nuclei feature vacuolization (Fig. 18.6a) with central vacuoles which appear either to be optically empty or to contain eosinophilic inclusions. Mitoses are scarce or absent. In some cases, there are circumscribed areas with a higher cell density, showing the appearance of growth centers, sometimes with mitoses (Fig. 18.6b).

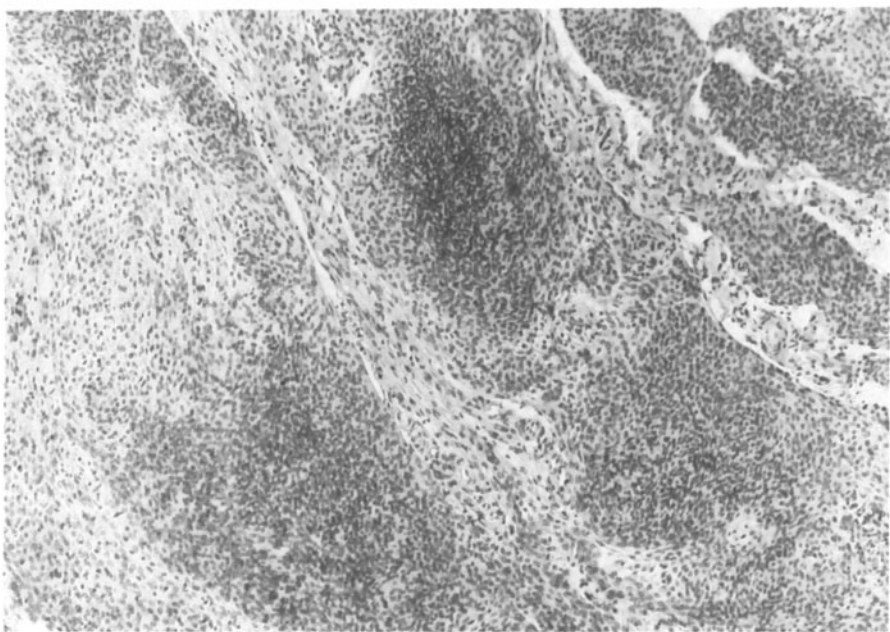
An interstitial collagenous stroma of variable density subdivides the neoplastic mass into the cell territories mentioned. Such stroma shows marked variability, not only from one tumor to the other, but also from one region to the next of the same tumor.



**Fig. 18.5a,b.** Meningioma. **a** General aspect with many lobules. H&E,  $\times 150$ . **b** Syncytial meningioma, ill-defined cell borders. H&E,  $\times 300$



a



b

**Fig. 18.6a,b.** Syncytial meningioma. **a** Vacuolated nuclei. H&E, ×300. **b** Areas with high cell density. H&E, ×200

It may be abundant, but especially in florid tumor areas, it is mostly sparse and limited. It contains thin blood vessels and a delicate framework of connective tissue. Reticular fibers are clearly confined to the stroma. In contrast to Mallory [2083] and Bailey [128], Klose [1718] never found free elastic fibers in the parenchyma, but only in relation with blood vessels.

Like nonneoplastic arachnoid cells, meningothelial cells can arrange themselves in a spiral fashion and form whorls (Fig. 18.7a). These may be occasional and isolated or occupy the entire neoplasm. Whorls are formed around the meningothelial cells, blood vessels, or other structures; collagenous fibers, which may stain for reticulin and collagen, may be deposited. They may undergo hyalinization and other phenomena connected with calcification, becoming psammoma bodies. These tumors have been called endotheliomatous, meningotheliomatous, or syncytial meningiomas.

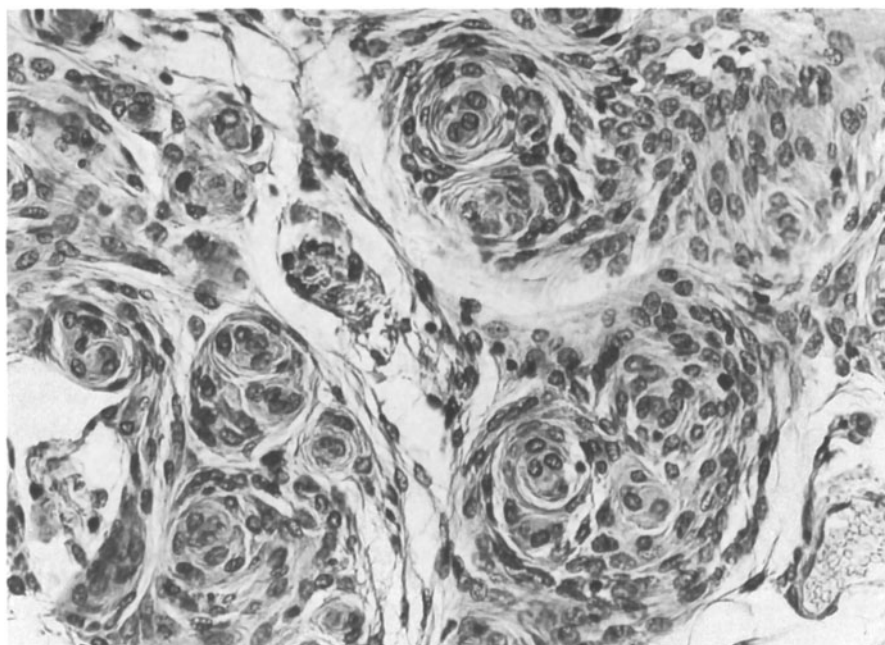
A different histological appearance, characterized by fusiform and elongated cells, arranged in interwoven bundles, morphologically similar to fibrocytes, may be present in some tumors (Fig. 18.7b). Whorls, although less common and less structured than in the previous type, are often formed, but they sometimes have a clearly perivascular arrangement. Psammoma bodies are observed less frequently and are, on the whole, less numerous. The nuclei, usually ovoid or elongated along the major cell axis, are similar to those of the previous type. Their occasional alignment should not be confused with the palisades of neurinoma. An important differential characteristic of fibroblastic meningiomas is represented by the richness in collagenous and reticulin fibers. The latter are particularly well developed and form a fine intercellular network; however, they remain confined to the septa and blood vessels and do not belong to the parenchyma, even if they appear in areas in which the reticulin network is present between the tumor cells. Tumors of this type are called fibroblastic meningiomas, even if extravascular reticulin usually does not appear. When the fibroblastic and syncytial appearances coexist, one may speak of transitional meningiomas. In both these tumor types, the expression of laminin and intercellular type IV collagen is controversial: Both positive [2198, 2477] and negative [191] results have been reported.

In general, meningiomas have a clear-cut boundary with the neural tissue (Fig. 18.8a) and may be considered encapsulated tumors, although this capsule is variable in thickness and may even be altogether lacking. It is formed by an arachnoid membrane, the pia, and the tumor stroma. The limit between tumor and healthy tissue has been classified as “smooth,” “fingerlike expansion,” “lobular”, and “invasive”. In the last type, the demarcation is poor, and invasion occurs along the Virchow–Robin spaces [2394].

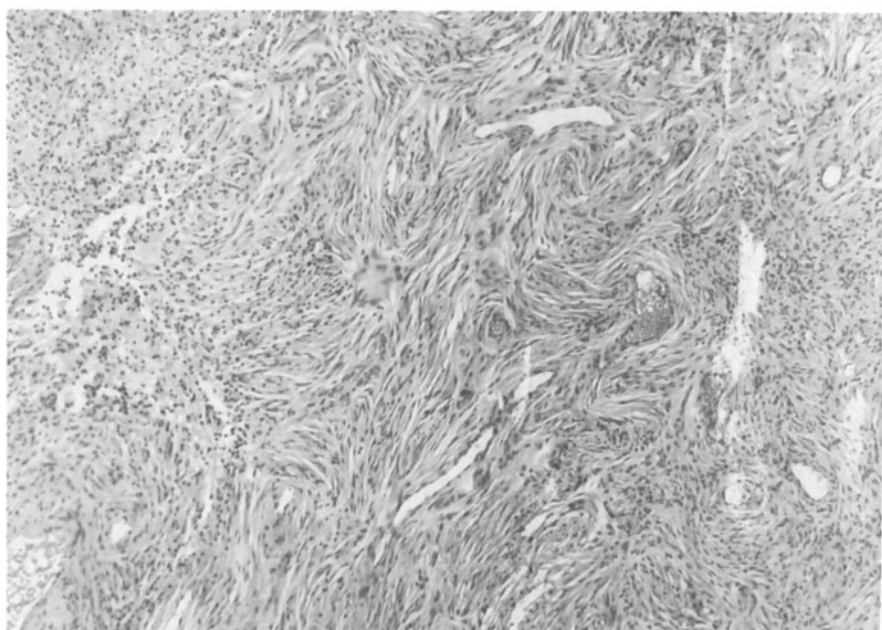
#### 18.1.12.1

##### *Angiomatous Meningiomas*

These are less frequent. Their main histological characteristic is represented by a spongy appearance, caused by a large number of blood vessel lacunae (Fig. 18.8b). The latter appear delimited by endothelial cells arranged in a single layer. In some cases, as in the angioblastic areas of the previous types, the angiomatous structure is very similar to that of hemangioblastomas from which these meningiomas must be



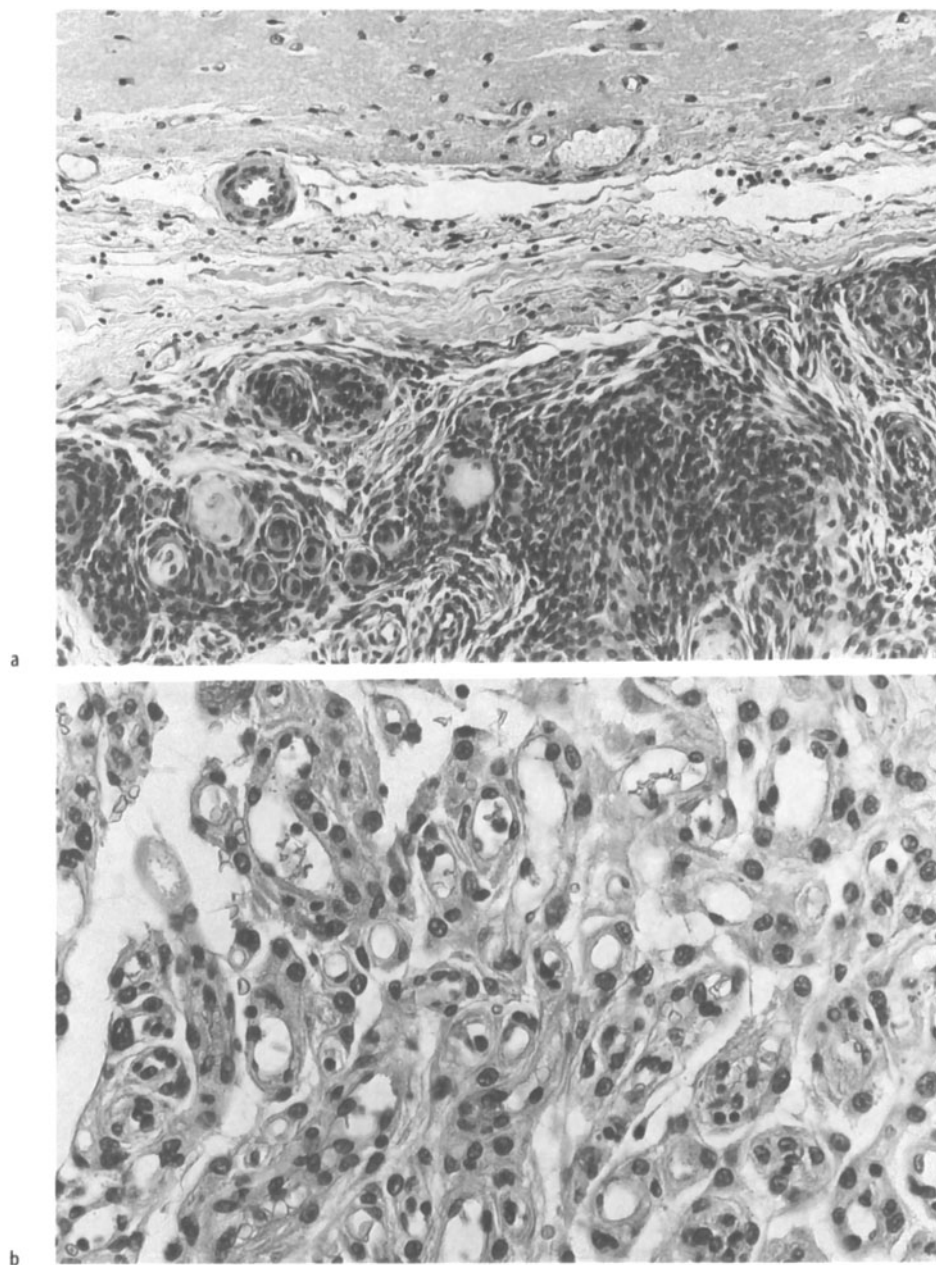
a



b

**Fig. 18.7a,b.** Meningioma. **a** Formation of whorls. H&E, ×400. **b** Fibroblastic meningioma. H&E, ×200





**Fig. 18.8a,b.** Meningioma. **a** Definite borders toward normal nervous tissue. H&E,  $\times 200$ . **b** Angiomatous meningioma. H&E,  $\times 400$

distinguished on the basis of light and electron microscopy findings. In hemangioblastomas, the blood vessel lacunae are mostly of irregular dimension and shape, from small capillary-type dilatations formed by one or two parietal cells to large, cavernous, irregular, and sinusoidal cavities. In angiomatous meningiomas, the rich vascularization, especially capillary, is not in strict relationship with the neoplastic elements. Endothelial cells frequently appear swollen, so as to occlude partially or totally the lumen of the blood vessel. The nuclei are generally more irregular than in the previous types, both in shape and in chromatin content. The presence of vacuoles is common to hemangioblastomas. Mitoses are occasionally observed.

The connective tissue stroma is formed by polygonal cellular elements, morphologically similar to the endothelium of the lacunae, and by an abundance of collagenous and reticulin fibers, which form a well compacted network with a mesh often corresponding to the blood vessel lacunae. In general, with respect to the previous tumor types, there is a greater tendency to cellular atypia and architectural disorganization. It should, however, be emphasized that in cases in which such characteristics are more evident, the biological behavior does not differ from that of other tumors of the same group which remain benign. It seems reasonable to interpret these morphological features as the consequence of regressive events rather than anaplastic ones.

Angiomatous meningiomas are common meningotheelial meningiomas, rich in blood vessels. Some tumors, however, have a different appearance: Small blood vessels are totally enveloped by tumor cells, and foamy cells are especially noticeable between the blood vessels, so that they resemble cerebellar hemangioblastoma. Whether this tumor is a hemangioblastoma or a hemangioblastic meningioma is still a matter open to discussion. It has been underlined that cells wrapped around capillaries are not characteristic of hemangioblastoma, but of meningioma. These tumors should not be considered as a hemangioblastic variety of meningioma, but rather as pure angiomatous meningiomas [1642]. There are tumors which have a structure typical of cerebellar hemangioblastoma, hemangioblastomas of von Hippel-Lindau disease [1642]. According to others, transitional forms between hemangioblastoma and angiomatous meningioma occur [2904].

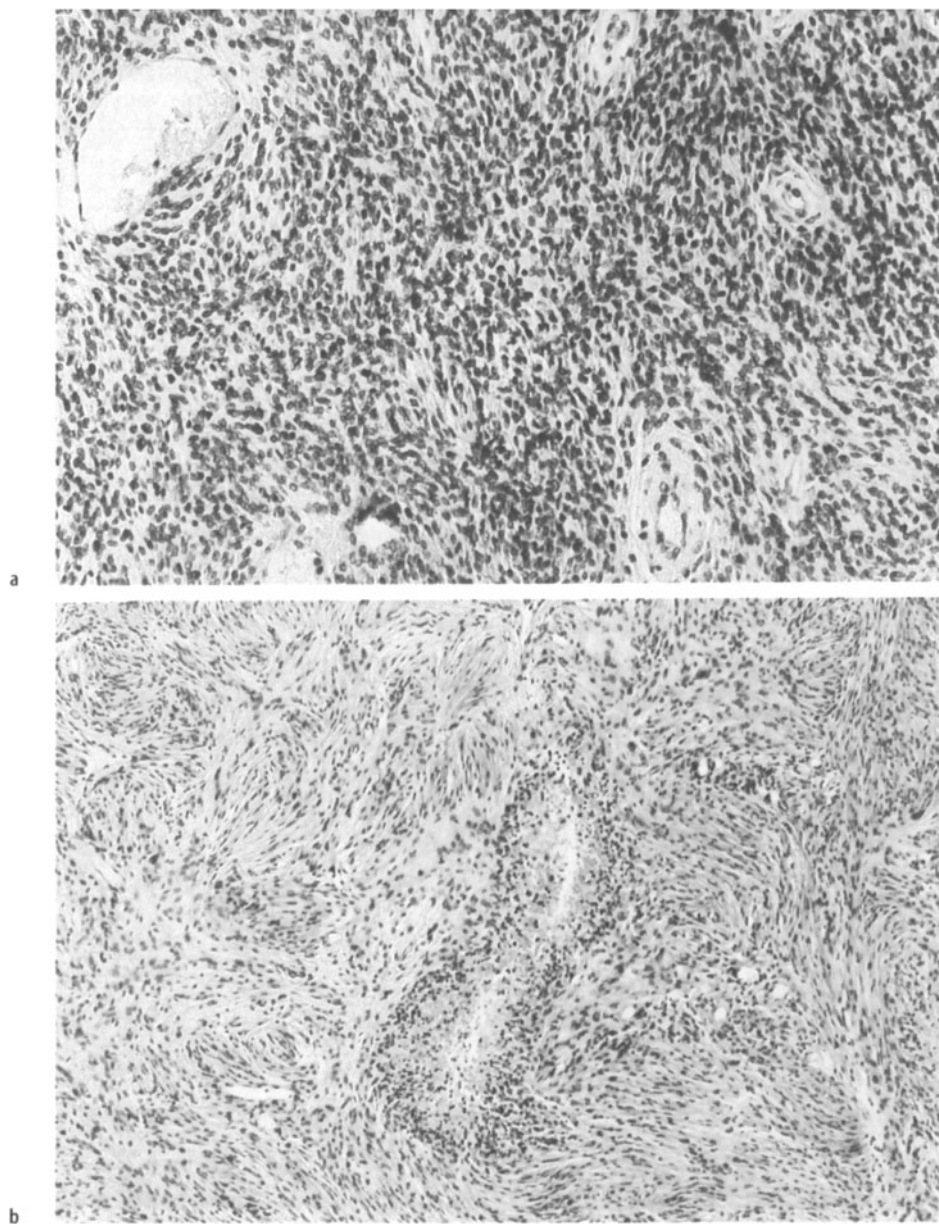
#### 18.1.12.2

##### *Malignant Meningioma*

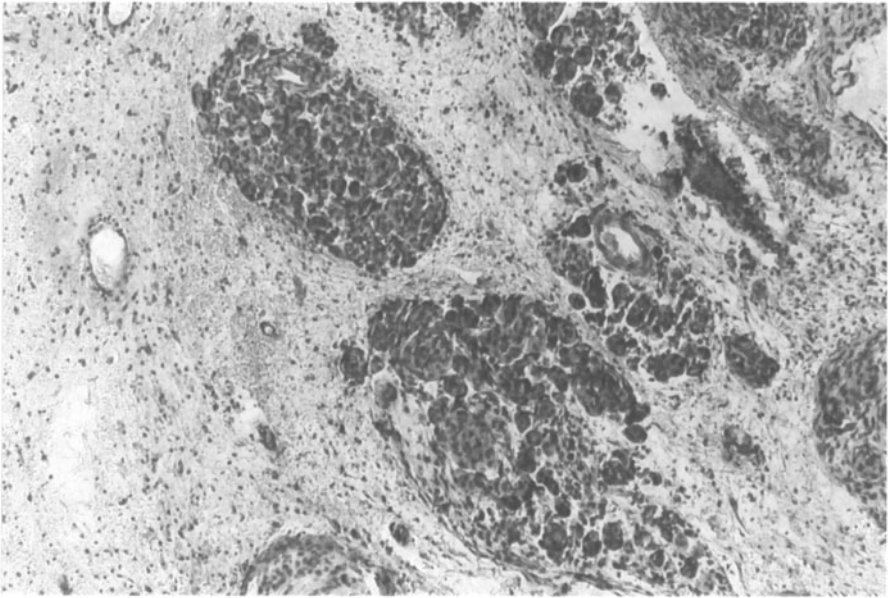
All types of meningiomas may be malignant. A high number of (atypical) mitoses [859], circumscribed necroses, infiltration of neural tissue [600], and high cell density [3214] are useful criteria of malignancy (Fig. 18.9). All of these signs have an undoubted prognostic value, even if they have to be evaluated with caution [1525].

The definition of tumor infiltration of the nervous tissue is not easy. While for some the “fingerlike expansion” of the interface between tumor and healthy tissue (Fig. 18.10a) is an expression of invasiveness [600], for others [2394] this is a sheer peculiarity of tumors without a definite border which infiltrate along the Virchow-Robin spaces. There may be real infiltrative growth (Fig. 18.10b).

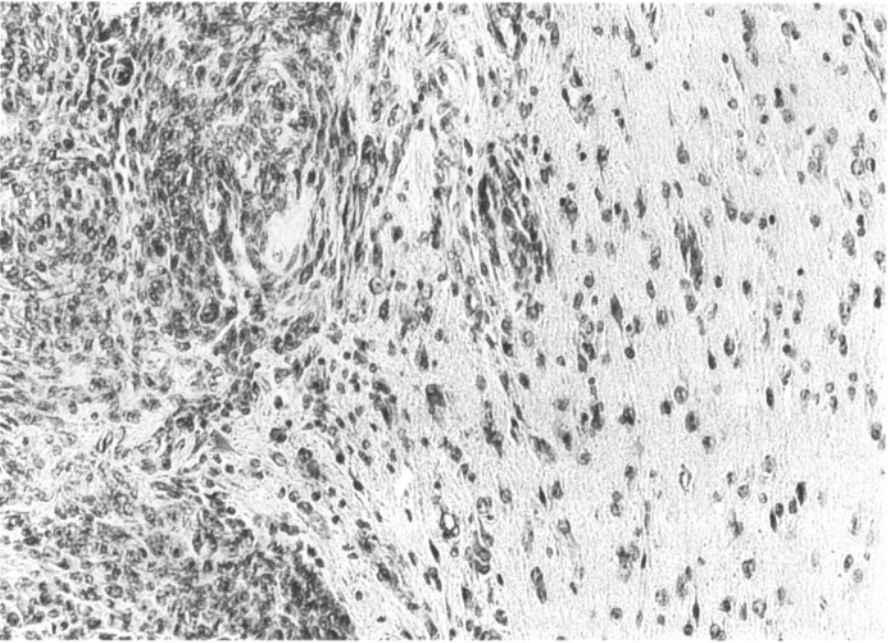
The definition of malignant meningioma is easy when all the signs of anaplasia are present at the same time.



**Fig. 18.9a,b.** Malignant meningioma. **a** Very high cell density and many mitoses. **b** Circumscribed necrosis. H&E,  $\times 200$



a



b

**Fig. 18.10a,b.** Meningioma. **a** Fingerlike expansion. **b** Infiltration of tumor cells in the normal nervous tissue. H&E,  $\times 200$

The WHO has established six parameters, on the basis of which a diagnosis of malignant meningioma may be made, but there may be more [2819]. However, it is difficult to identify the malignant variant when it has to be decided on a quantitative basis or when only some signs are present. There are, in fact, contradictory observations when histological features are compared with survival data. Automatic image analyses have demonstrated that neither the nuclear nor the cell density are prognostic elements. The histological type is also not predictive, while recurrences are more frequent in young subjects, in males, and in parasagittal sites. Circumscribed necroses and bony infiltration are more frequent in recurrent meningiomas, while cortical invasion is not significant [517]. According to others, anaplasia with typical and atypical mitoses would be more indicative than necroses and invasion of healthy neural tissue [3424]. The topic will be taken up again in the discussion on prognosis. It is, however, useful to recall that, using the six histological above-mentioned parameters of the WHO, meningiomas have been classified into four grades with increasing malignancy: benign, atypical, anaplastic, and sarcomatous.

Atypical meningiomas would be characterized by increased cell density, mitotic rate, and nucleocytoplasmic ratio, prominent nucleoli, and areas of necrosis [2976]. In addition, malignant meningiomas show invasion of the underlying nervous tissue. This classification has been found to correlate well with the tumor doubling time [1481] and also with radiological features. In particular, it has been observed that the recurrence was 3% for benign, 38% for atypical, and 78% for anaplastic tumors, with recurrence times of 7.5, 2.4, and 3.5 years, respectively [1482]. Another suggestion is to identify malignant meningioma on the basis of high cell density and nuclear polymorphism, associated with one of the other negative prognostic signs such as mitoses, necroses, invasion of neural tissue, papillary features, and hemangiopericytic variant [490].

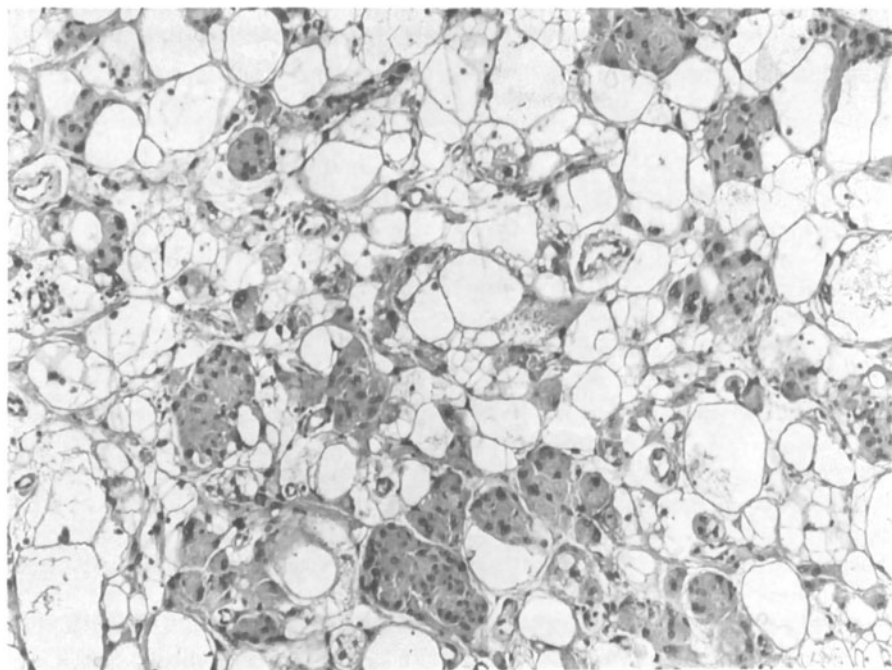
Malignant transformation may also occur during the biological life of a meningioma, as may be found with repeated operations [1914]. This probability of transformation has been estimated to be 14% [1482].

The papillary variant has to be considered with the malignant variant, because the former is usually found in tumors which show an unfavorable biological behavior [333, 2566], tend to recur, and produce distant metastases [2039]. For others, instead, it is a secondary phenomenon, without clinical and biological significance [3290]. The papillary appearance is due to the arrangement of the cells in relation to blood vessels and to the relaxation of the intervascular tissue. It may appear in any type of meningioma, although it is more common in the hemangiopericytic variant and at younger ages [2904]. This variant gives serious problems in the differential diagnosis with regard to other tumors, either neuroectodermal, mesodermal, or secondary. Immunohistochemistry testing is, without a doubt, of great help.

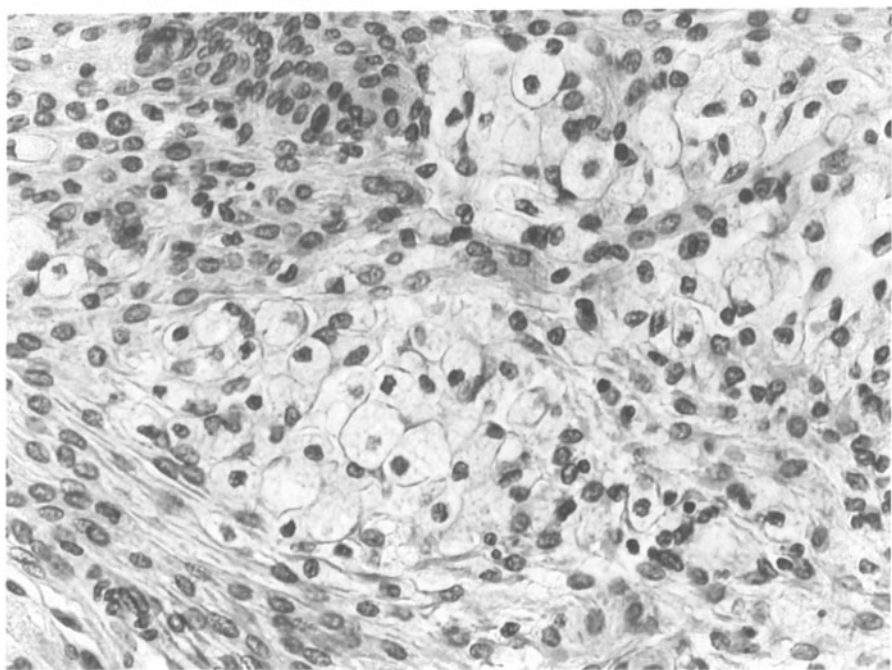
### 18.1.13

#### Metaplasia in Meningiomas

An event occurring with variable frequency is lipoblastic metaplasia. Fat droplets accumulate in the cytoplasm and, by confluence, transform the cytoplasm into a single droplet of fat with a peripherally situated nucleus, as in adipocytes (Fig. 18.11a). It



a



b

Fig. 18.11. a Lipoblastic meningioma. b Xanthomathous meningioma. H&E,  $\times 300$

should not be mistaken for fatty degeneration. Various authors disagree on the real existence and on the frequency of this variety, which seems rather unusual and is not considered in some series [1874]. Single cases have been reported [1920, 2933].

In xanthomatous metaplasia one observes foamy cells with a central nucleus and cytoplasm filled with fine vacuoles, in transition from normal tumor cells (Fig. 18.11b). These cells have to be distinguished from phagocytic or perihemorrhagic and perinecrotic cells.

It has been demonstrated, however, that these cells express antigen that are typical of histiocytic macrophages, even though they are not present in neoplastic meningotheelial cells. The aspect of a cell depends, therefore, not only on its histogenesis, but also on its activity [1645].

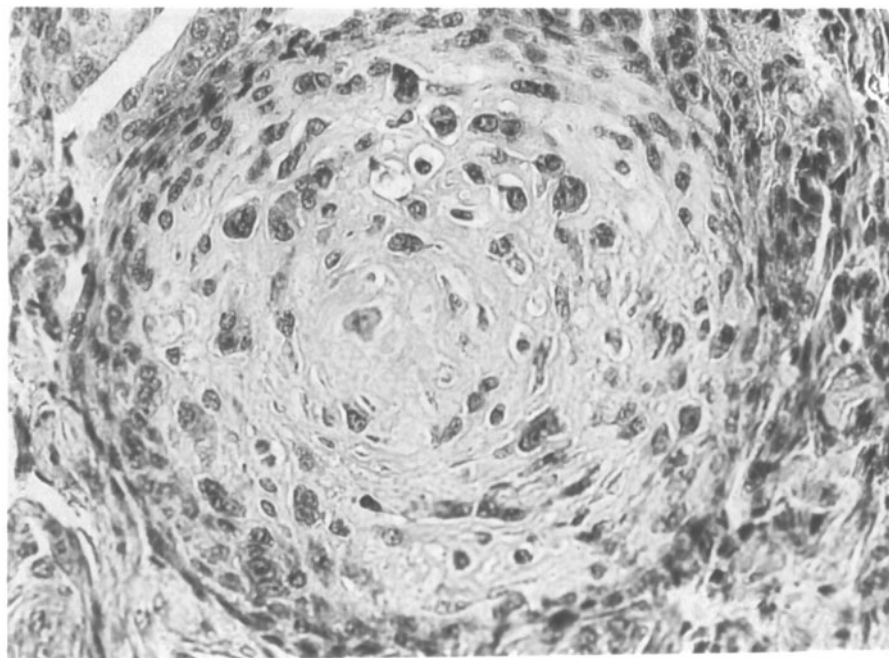
Myxoid and chondroid transformation are not rare and are often associated (Fig. 18.12a). The former gives to the tumor a diffusely mucinous appearance, which recalls the "primitive mesenchyma." There is diffuse positivity for glycosaminoglycan (GAG) [1246]. This variant is very close to the microcystic one, characterized by the presence of many vacuoles and microcysts filled with proteinaceous fluid.

A chondro-osteoblastic transformation is also considered. The presence of cartilage in meningiomas is a very rare occurrence, so it would be unjustified to describe a separate category of chondroblastic meningiomas [3800]. Even though the formation of bone is a rare finding, an osteoblastic variant has been described [131, 629, 955, 1297, 670] and accepted by some, but denied by others [1099]. Although bone formation is possible in all types of meningioma, sometimes in relation to calcified psammomatous bodies, the justification for a distinct variety of osteoblastic meningioma is rather doubtful [2904]. The formation of bony structures in meningeal tumors has at least two pathogenetic possibilities [856]: through a process of metaplasia of the tumor, arachnoid cells, or the stromal connective tissue or through ossification secondary to a process of calcification. There is general agreement as to the first pathogenetic modality, because the arachnoid tumor cells are relatively undifferentiated elements capable of producing, under suitable circumstances, fibroblasts, osteoblasts, and osteoclasts. Phenomena of metaplastic ossification from collagen are observed in various extraneural sites and in various pathological conditions. The formation of bone could represent the final stage of the process of calcification. Pseudocalcium and hydroxyapatite production up to the formation of bone are, in fact, related to the processes of *kalzifizierende Organisation* [279] and *knöcherne Organisation* [1789].

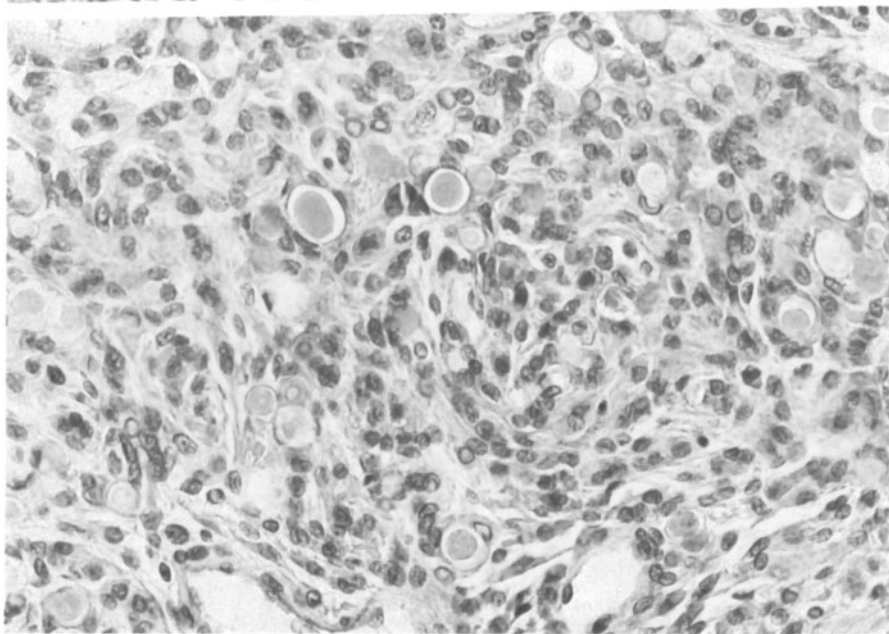
Sometimes, strongly eosinophilic periodic acid-Schiff (PAS)-positive inclusion bodies, called "pseudo-psammoma bodies" (Fig. 18.12b), are found in the parenchyma of meningotheliomatous meningiomas [1637]. They have been described in a limited number of cases [1140] and found to be similar to hyaline globules of other tumors. They have been interpreted as evidence of a possible secretory differentiation of meningiomas [1639]. From the immunohistochemical point of view, they have been observed to be positive for the human secretory components immunoglobulin A (IgA) and IgM [374], cytokeratin, vimentin, epithelial membrane antigen (EMA), and carcinoembryonic antigen (CEA) in the surrounding cells [3416, 2228, 1140].

Melanin-containing tumors of the leptomeninges deserve to be mentioned. The finding is not infrequent and usually occurs in tumors of the posterior fossa or the spinal canal (Fig. 18.13a). The problem is complicated by the fact that in some cases





a



b

Fig. 18.12a,b. Meningioma. a Myxochondroid metaplasia. b Pseudopsammoma bodies. H&E,  $\times 400$



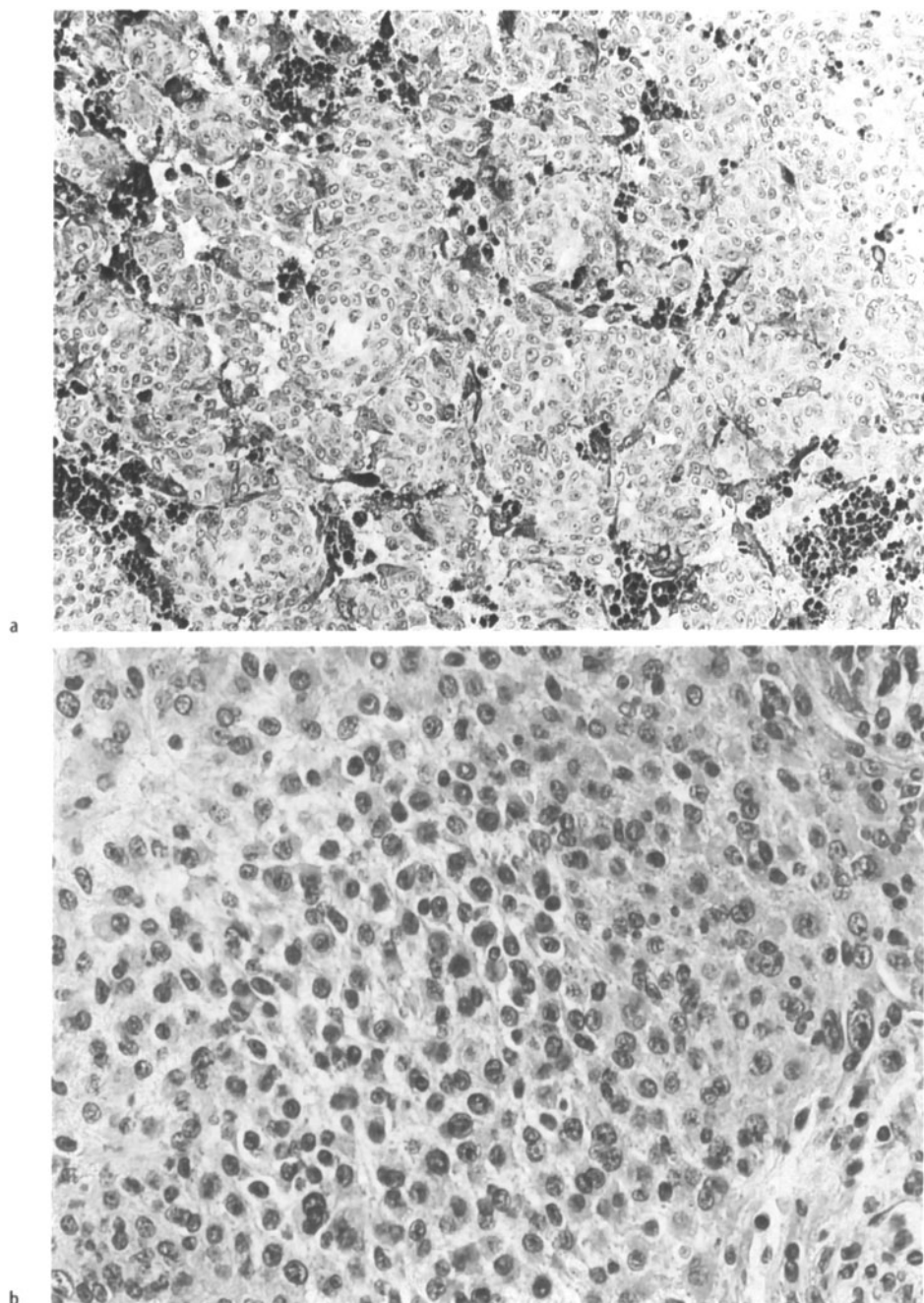


Fig. 18.13. a Melanin-containing meningioma. H&E,  $\times 200$ . b Lymphoplasmacellular infiltration. H&E,  $\times 300$

they could be melanocytomas rather than meningiomas, arising from nevus cells of the leptomeninges [1962, 3699]. However, there appears to be no doubt concerning the existence of classical meningiomas containing melanin [3474, 1642].

In meningiomas, it is not rare to find lymphocytic and plasmacytic infiltrates, both diffuse and perivascular. The lymphocytes are of the T subset, an expression of immunological defense mechanisms, and are found with greater frequency in the anaplastic variant than in meningotheiomatous and fibroblastic meningiomas [182]. Independent of these observations, there is a group of meningiomas which is characterized by a large number of lymphocytes and plasma cells (Fig. 18.13b) obscuring the meningiomatous component [1397, 3282, 1642, 2283, 2904]. Raised levels of IgG have been found in the serum of these patients. In one, there was a high blood level of IgG and IgA, which dropped after surgical removal of the tumor [1063]. Tumor infiltrates are activated B lymphocytes and plasma cells (of inflammatory and not of tumor origin), whose polyclonality has been demonstrated immunohistochemically [3282, 2283]. The nature of the association is not clear [2904]. The possibility may be excluded that it is a plasma cell granuloma with included meningeal elements [3653], because of the extent of the meningotheial areas [1642]. Lymphoplasmacytic infiltrates have recently been found in meningiomas, with a chordoid appearance in children and adolescents [1656].

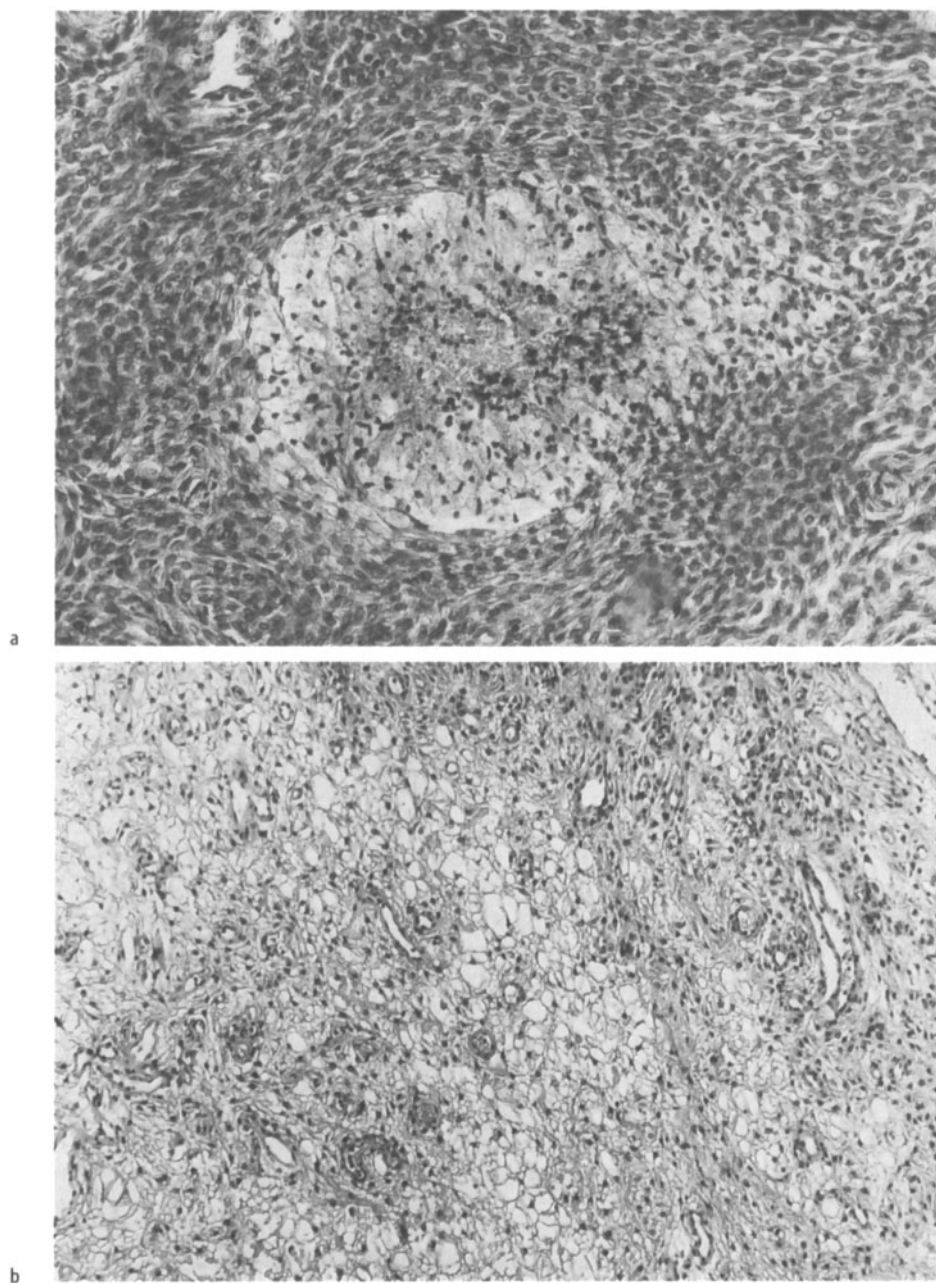
#### 18.1.14

##### **Regressive Changes**

Regressive changes in meningiomas are so frequent as to constitute one of the main features of this oncotype. This frequency, together with the multiplicity of processes, has been the main reason for the description of many varieties and subgroups. Also, the cellular polymorphism, sometimes simulating the anaplastic features of malignant tumors, is often due to regressive changes which typically present with features of great variability from tumor to tumor and from area to area of the same tumor. The changes are degenerative in nature, corresponding to the various processes of metamorphosis of general pathology (vacuolar, albuminoid, adipose, and mucosal) and to the typical vascular necroses. They may also be due to various storage processes.

Ischemic necrosis here does not differ in its appearance from that seen in other tissues. In general, it presents with the picture of granular degeneration of the cytoplasm, less frequently with that of tumor liquefaction. In parallel, the nuclei demonstrate regressive changes with pyknosis, karyorrhexis or karyolysis. In some meningiomas, particularly the syncytial type, necrosis is found at the center of a lobule, decreasing centrifugally (Fig. 18.14a).

In all the basic types described, but especially in syncytial meningioma, vacuolar degeneration may particularly involve the nucleus, where it presents as one or two large central or eccentric vacuoles. In the cytoplasm, instead, it shows a granular pattern. Sometimes, fluid accumulation goes beyond cellular swelling, causing hydropic swelling of the tissue, with cyst formation. In these cases, the process of tissue liquefaction is likely to be the result of a true accumulation of fluids (Fig. 18.14b), as occurs in some forms of edema in other tissues. The phenomenon may be extended to



**Fig. 18.14a,b.** Meningioma. **a** Ischemic necrosis at the center of a lobule. **b** Fluidification of tissue. H&E,  $\times 200$

the whole tumor, giving a variety of microcystic meningioma, the so-called *ménin-giome humide* of Masson [2144, 514, 2303, 1708, 2253, 2908]. This, however, does not seem to be of particular biological significance [2904].

Hyaline degeneration certainly represents one of the most common and most typical occurrences in meningiomas. It can involve all the structures of the tumor, from the parenchyma (Fig. 18.15) to the stromal connective tissue, to blood vessels (Fig. 18.16), etc., but, in its most frequent form, it starts in the whorls and proceeds centripetally.

Fatty degeneration is a fairly frequent event and when it results from other regressive cellular events, appears as colliquative foci rich in lipidized phagocytes in various stages of degeneration. In the phagocytic cells, the cytoplasmic borders disappear, and the nuclei undergo regressive changes. The phagocytosed lipids are formed by isotropic and sudanophilic material with the histochemical features of neutral fats and fatty acids.

Pseudoglandular structures, resembling adenocarcinoma, may form [1653], as the result of the degeneration of the center of the cell nests.

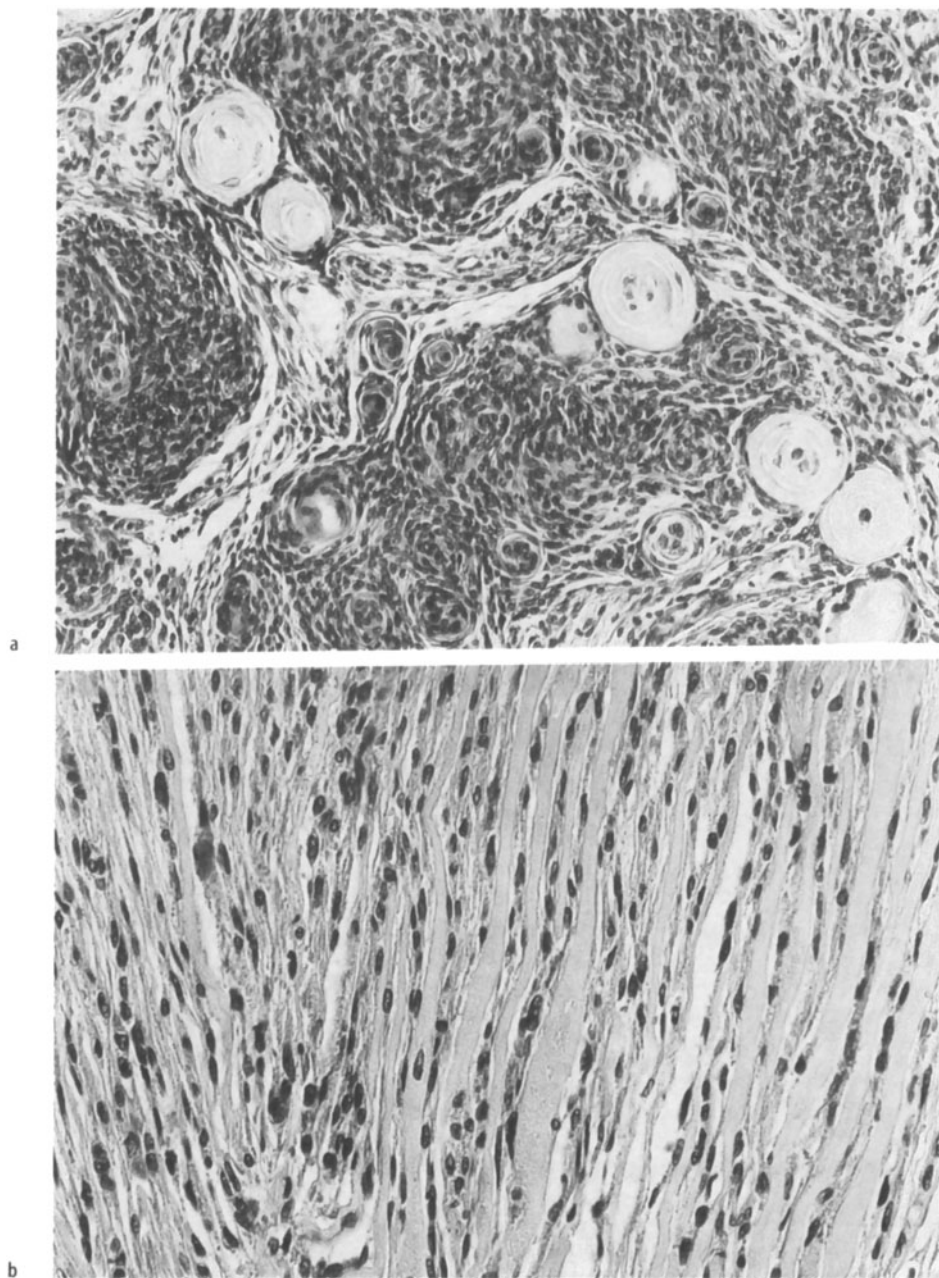
### 18.1.15

#### Calcifications

Calcification is one of the most frequent regressive events. It leads to the formation of psammoma bodies, a term coined by Virchow in 1900. From the earliest observations, a clear tendency of all meningioma variants to develop these structures has been noted. In some tumors, it is so marked as to justify the recognition of a “psammomatous” type. As first commented upon by Bailey and Bucy in 1931, it has the same origin as the endotheliomatous type with which it was then grouped. In the past, a great debate arose on the blood vessels of parenchymal origin in the psammoma bodies. According to some [1099], they were formed by vascular buds with a blind end. Others [852] recognized six pathogenetic possibilities, in each of which the fundamental process was represented by a mostly hyaline regressive alteration of the parenchyma and of the stroma. Still others [1874] considered the majority of psammoma bodies to originate from the transformation of a whorl.

Electron microscopy and in vitro cultures demonstrated that the fundamental process in the genesis of psammoma bodies consists of two main factors: the tendency of the meningotheelial cells to form whorls and the production by the same cells of a proteinlike material [1636] which tends to impregnate whorls, blood vessels, and collagenous stromal fibers. Histochemically, it has been identified as a protein-GAG complex.

Some cellular whorls neither hyalinize nor calcify; others are impregnated with a hyaline-like substance and organize into classical psammoma bodies [1637], on which mostly calcium salts precipitate. The production and deposition of the hyaline substance may be found in intra- and extracellular accumulations on which, in the absence of concentric cellular structures, the so-called pseudo-psammomatous bodies organize. Although the majority of psammoma bodies show a parenchymal genesis, there certainly are structures of the same appearance which form and organize in the stroma, in particular around blood vessels [1718]. This possibility has also



**Fig. 18.15a,b.** Meningioma. **a** Hyaline degeneration of whorls. H&E,  $\times 200$ . **b** Hyaline degeneration in fibroblastic meningioma. H&E,  $\times 400$

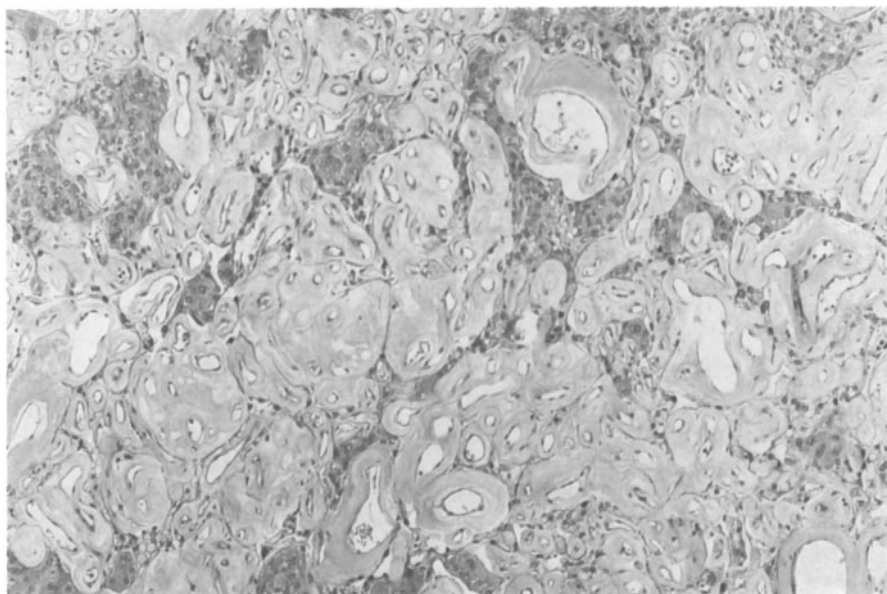


Fig. 18.16. Meningioma, hyaline degeneration of vessels. H&E,  $\times 200$

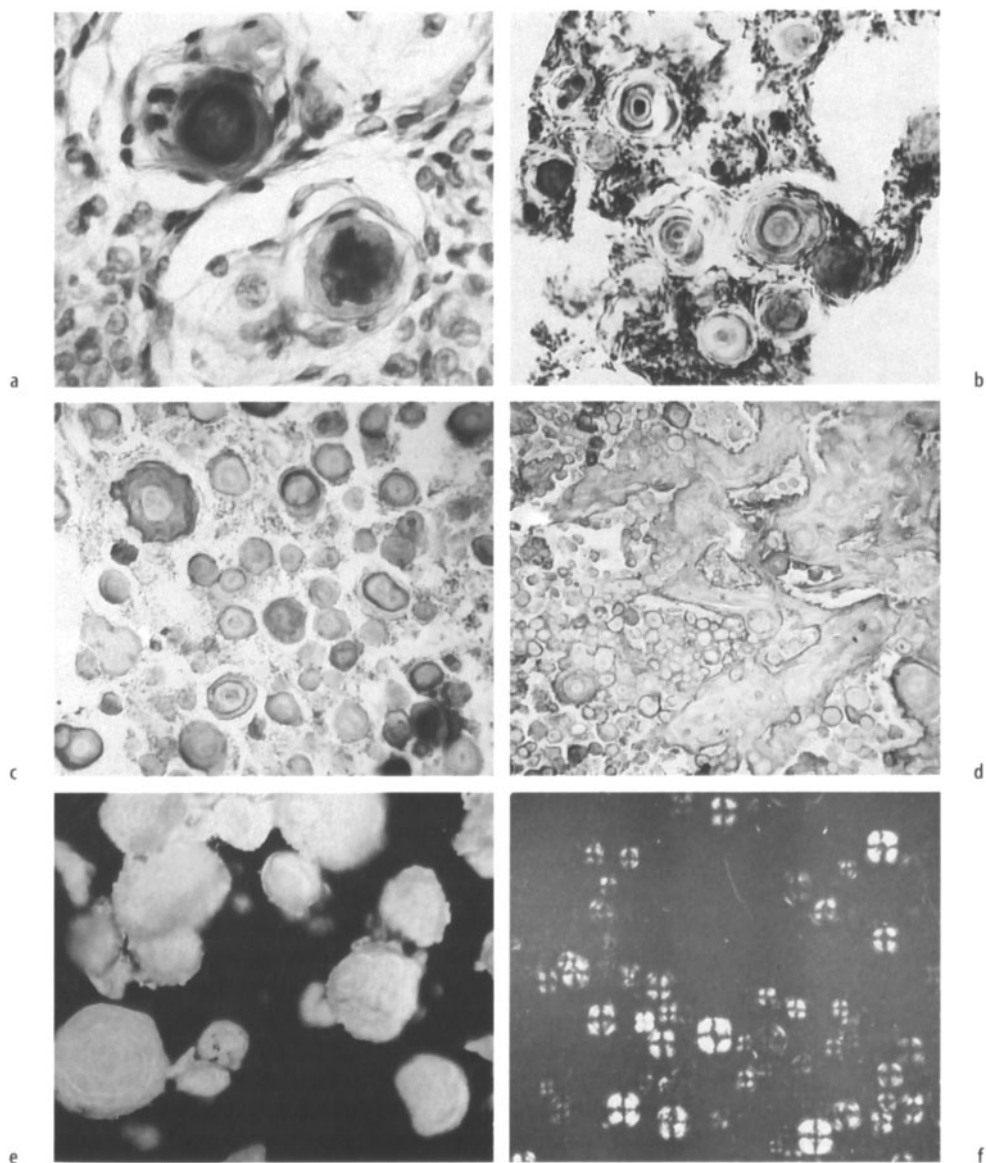
been raised on the basis of electron microscopic observations but is less frequent than the origin of the psammoma bodies from cell whorls [1132].

The appearance of calcifications in meningioma is a frequent event radiologically, and even more so histologically. In surgical and autopsy series, the histological frequency of calcifications is greater: According to Martin and Lemmen [2131], it reaches 18%, Schiffer et al. [2999] found 50%, and Huh [1429] 37.7%. The greater incidence obviously occurs in meningiomas of psammomatous type. For spinal locations, the frequency is higher.

Calcifications may occur as single concretions or in foci of concretions which sometimes tend to become confluent in larger, more or less regularly polycyclic and stratified formations [1835, 852]. The size of these conglomerates sometimes reaches enormous dimensions [2053]. In one personal case, the masses of calcified and conglomerated material formed the main part of the meningioma, which was larger than a fist. In this case, calcification developed primarily in the whorls and the fibrous connective tissue [857].

The morphology and site of the calcifications are variable and consist of four fundamental precipitation patterns (Fig. 18.17):

1. In the necrotic and preneurotic zones as fine, dustlike, hematoxyphilic material, whose distribution is independent of the preexisting parenchymal structures
2. In the blood vessel walls, a rare eventuality which more frequently occurs in the media and/or adventitia of arteries
3. In the whorls, particularly in meningiomas of the endotheliomatous type
4. In the fibrous bundles of fibroblastic meningiomas



**Fig. 18.17a–f.** Calcification in meningioma. **a** Basophil pseudocalcium-calcium (pCa-Ca) deposition in whorls. H&E,  $\times 400$ . **b** pCa-Ca deposition in the whorls; further evolution of the process. Cresyl violet,  $\times 200$ . **c** Psammomatous bodies with variable basophilia. Toluidine blue,  $\times 200$ . **d** Calcified and confluent whorls. Toluidine blue,  $\times 400$ . **e** Microincineration of psammoma bodies at  $550^{\circ}\text{C}$ ,  $\times 400$ . **f** Maltese cross of polarization in calcified whorls. Polarized light,  $\times 200$ . (From [2994])

In the whorls, the dynamics of the calcification process follow two possibilities (see also Chap. 5). A delamination of the whorl separates its external layers, which acquire a fibroannular appearance. The internal concentric layers are reduced to some cell elements with pyknotic nuclei and irregular cytoplasm. Subsequently, small droplets of pseudocalcium appear which tend to become confluent in irregular, intensely basophilic, PAS-positive masses. In this phase, calcium salts are already present. The mass becomes progressively rounded and, whilst its external part reacts more intensely with the methods mentioned above, the internal one shows a concentric stratification because of the alternation of clear and dark rings. The pseudocalcium ends up occupying the whole of the central part of the whorl by adhering to the fibroannular part. At this stage, calcium salts predominate and the concentric stratification is very evident. As mineralization progresses, there is a progressive impoverishment of the organic matrix, as revealed by the reduction in the basophilia. In the terminal stages, the concretion appears vitreous and may become fragmented [2999].

The second mechanism of calcification of the whorls is the appearance of hyaline degeneration, followed by the precipitation of pseudocalcium. The subsequent evolution of the process repeats the stages already described. The concretion is surrounded by a hyaline ring during the whole process.

In general, the process of calcification in meningiomas does not demonstrate substantial differences in respect to that of other calcifying events in the CNS [3001, 3003, 1958]. Calcium phosphate is deposited in a complex form as hydroxyapatite [2988]. It is possible that the GAG matrix is provided by mast cells, which are important in many spontaneous and experimental calcifying conditions, such as processes of calcercgia and calciphylaxis [3126]. In the meninges, mast cells are very common [1662]. They have frequently been observed in meningiomas and related to the mucoid degeneration [3799]. They may be scarce or abundant, often distributed at the periphery of the tumor, along the interlobular septa, along blood vessels, or even deep in the parenchyma, irrespective of the structures of the tumor, or in the center of a whorl. In this particular site, they may show a dispersion of the metachromatic granules and form the substrate for the precipitation of calcium salts, being rich in sulfated GAG [3007].

Under the electron microscope, there are corresponding observations. In the whorls, extracellular spaces between the central and peripheral cells contain amorphous material, collagen fibers, microfibrils, elastic fibers and reticular material resembling proteoglycans. In this material there are calcified areas (Fig. 18.18), foci or aggregates of apatite crystals oriented along the collagen fibers. At the periphery of the psammoma bodies there are spherical bodies similar to the vesicles of the matrix, typical of calcifying tissues with rare apatite crystals [62]. Such vesicles seem to originate from cell processes of the central cell in the whorl. The accumulation of these structures gives rise to the psammoma bodies [1793, 1794, 1795]. The same process occurs for psammoma bodies forming around blood vessels in which vesicles form from degenerated cells in perivascular spaces [1796, 1798].

On plain X-rays, calcifications show an amorphous, cloudy aspect. They are less frequent than in pathological series (>10%) [3401, 769]. On CT study, calcifications appear as nodular foci and are more frequent in the posterior fossa [2419] and less common in malignant meningiomas [1482]. On MRI scans, calcifications are seen as black areas [323].



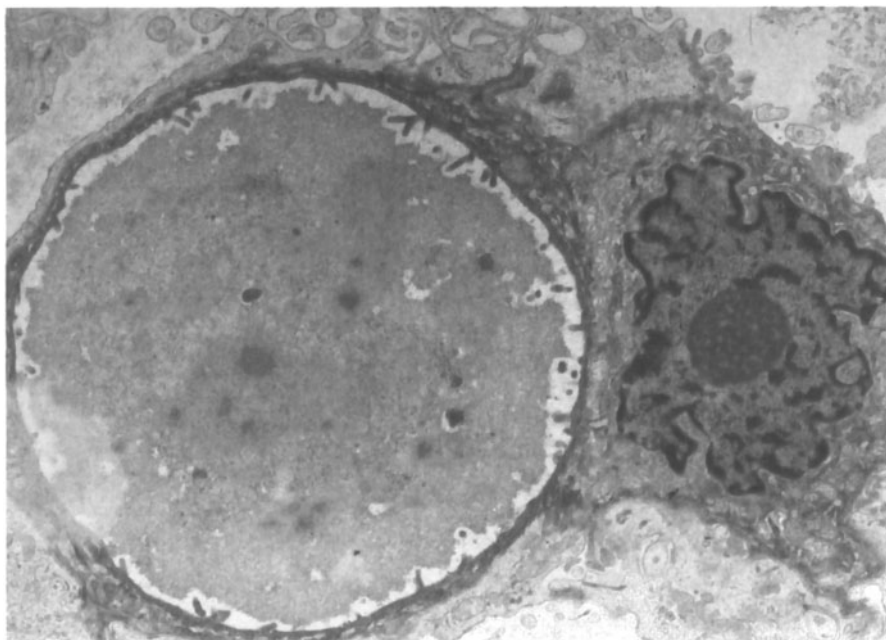


Fig. 18.18. Calcification focus in a whorl. Uranyl acetate, lead citrate stain,  $\times 8000$

#### 18.1.16

##### Electron Microscopy

Numerous contributions from electron microscopy studies have been made in the past 30 years [2048, 1636, 1199, 2715, 1132, 2396, 2808, 450, 466, 3388, 1639, 2805, 569, 472]. The most important finding is the extreme interdigitation of the cell membranes, similar to that of the normal arachnoid cells, which explains the syncytial appearance (Fig. 18.19). Among the cells, desmosomes or other junctions and cistern-like spaces occur. This explains why the cell borders are not easily recognizable with the light microscope. The whorls are easily identified, sometimes with a capillary in the center. Tonofilaments, often arranged in a spiral, are present in the cytoplasm. Cilia may be found, even if not protruding, but contained in the cytoplasm. It may happen that the cells are not adherent to each other, and granular and osmiophilic material interposes itself between the cell membranes. Often, it is in continuity with filamentous material corresponding to protocollagen and mature collagen fibers [1636].

The hyaline material, which is often found under the light microscope in the center of the whorls, appears to be formed by residues of degenerated endoplasmic reticulum, lysosomal components, and mitochondria. In it, hydroxyapatite crystals appear [1976]. In the vessel walls, an abundant production of collagen fibers can be found (Fig. 18.20).

Nuclear inclusions are formed by invaginated and sequestered cytoplasm. There are also other types of inclusions, such as dense and osmiophilic nuclear ones [2808] or floccular material without membranes. Filamentous spheroid structures may be

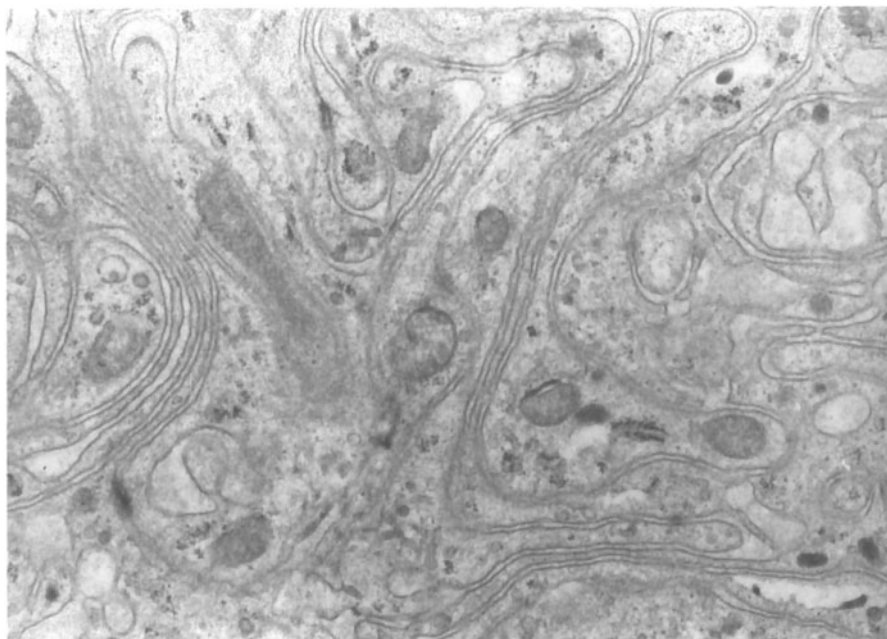


Fig. 18.19. Syncytial meningioma, interdigitating processes and small desmosomes. Uranyl acetate, lead citrate stain,  $\times 24000$

found [466]. Eosinophilic inclusion bodies correspond to granular material, situated in an intracellular cavity similar to a duct, delimited by microvilli which contain the same type of material [1636].

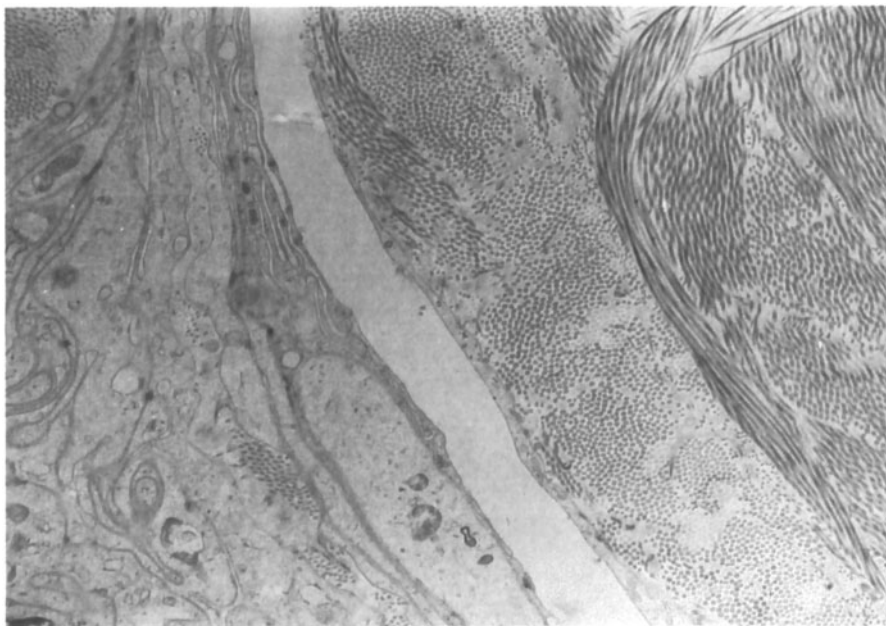
#### 18.1.17

##### Receptors for Steroid Hormones

Meningiomas are more common in females and increase in incidence in pregnancy and during the luteal phase, but not in the proliferative phase of the menstrual cycle [1921]. Furthermore, as already mentioned, they have been reported in association with breast carcinoma, although this has not been fully established [3076].

Estrogen receptors have been identified in meningioma [751], but more obvious is the presence of progesterone receptors, because they are numerous and present in a larger number of patients [2656, 3439]. These data have been confirmed by numerous authors. Some have even found androgen receptors [1922]. Notable uncertainties, however, still remain as to the correlation between receptors of one or the other steroid type with age, sex, and histological type [1469] and as to whether the receptors are really functional [1323, 982]. That receptors intervene in the tumor growth has been demonstrated *in vitro* [2498], even if our knowledge needs, at this point, further data [2120].

Using high-affinity progesterone-specific antibodies, it has recently been demonstrated immunohistochemically that the receptors truly exist and are not simple progesterone-binding proteins [3098]. This could render the meningioma amenable to



**Fig. 18.20.** Atrophic endothelium and abundant collagen fibers in a vessel wall. Uranyl acetate, lead citrate stain,  $\times 8000$

manipulation with hormones [2121, 3581]. The presence especially of progesterone receptors and to a minor degree of estrogen receptors has been ascertained by using many methods at the same time, among them the nuclear binding assay [3269] and some of these are functional [1228]. Other investigations demonstrated, however, that there is no correlation between the presence of progesterone, estrogen, and somatostatin receptors and age, sex, histology, and behavior on CT [1430].

Using quantitative methods, high levels of progesterone receptors and low levels or absence of estrogen receptors have been found [1179]. By quantitative immunocytochemical methods in 52 meningiomas, it has been found that estrogen receptors are lacking and that tumors showing progesterone receptors differ from the clinicopathologic point of view from negative tumors. In some tumors, estrogen-regulated protein has been found [316].

#### 18.1.18

##### In Vitro Culture

In the first attempt to culture meningioma in vitro, it was observed that cells grew easily and that typical primary structures, for example whorls, were lacking [266]. Subsequent studies, however, demonstrated that such structures may be produced ex novo [2663, 577, 1666, 2043]. It has been found that while meningiomas in a standard culture of plasma show a scarce or no capacity to form whorls, their potential ability

to form them may easily be revealed with simple changes of culture conditions, e.g., employing trypsinized suspensions of arachnoid tumor cells [1666]. According to these authors, concentric structures were the result of a primary deformation of a single cell, forming the regulatory center of the whole process, which occurs because of successive adaptation of the adjacent cells.

The growth in culture never shows the characteristic morphological differences observed among the main types described by histology, so that the histological terminology cannot be directly applied. The explant usually manifests its maximal proliferative activity during the first week. In this phase, at the periphery, elongated cells similar to fibroblasts of normal leptomeninges prevail, but sometimes they show more than two prolongations and arrange themselves in moniliform chains or in concentric formations. This tendency to concentric arrangements is more marked in the center of the explant where rudimentary whorls or syncytial structures may be found. Intra- and extracellular fibrils are observed, particularly where the growth is syncytial. They show features of precollagen reticular fibers [577, 578].

The recognition of various cell types is difficult. They may be small, bipolar, elongated cells with hyperchromatic nuclei; cells of medium size with large, oval nuclei, often in mitosis and tending to grow as a syncytium; or larger cells with extended cytoplasm containing one or more nuclei [2332]. In the last instance, mitoses are never observed, whilst amitotic divisions are frequent. The cells of the second type are, in general, the real tumor cells and represent the main part of the explants. In 19 cases, neither whorl formation nor differences between endotheliomatous and fibroblastic meningiomas were observed. With the utilization of microcinematography recordings, the formation of small rudimentary whorls was observed, sometimes presenting hyalinization and calcification up to the formation of psammoma bodies [2664]. Initially, these structures show complex rotatory movements of "peristaltic" type. With the same technique, it was also possible to observe that some of the neoformed whorls were undergoing disaggregation. The growth in culture permits one to distinguish between disorganization and reorganization of the architecture [2520].

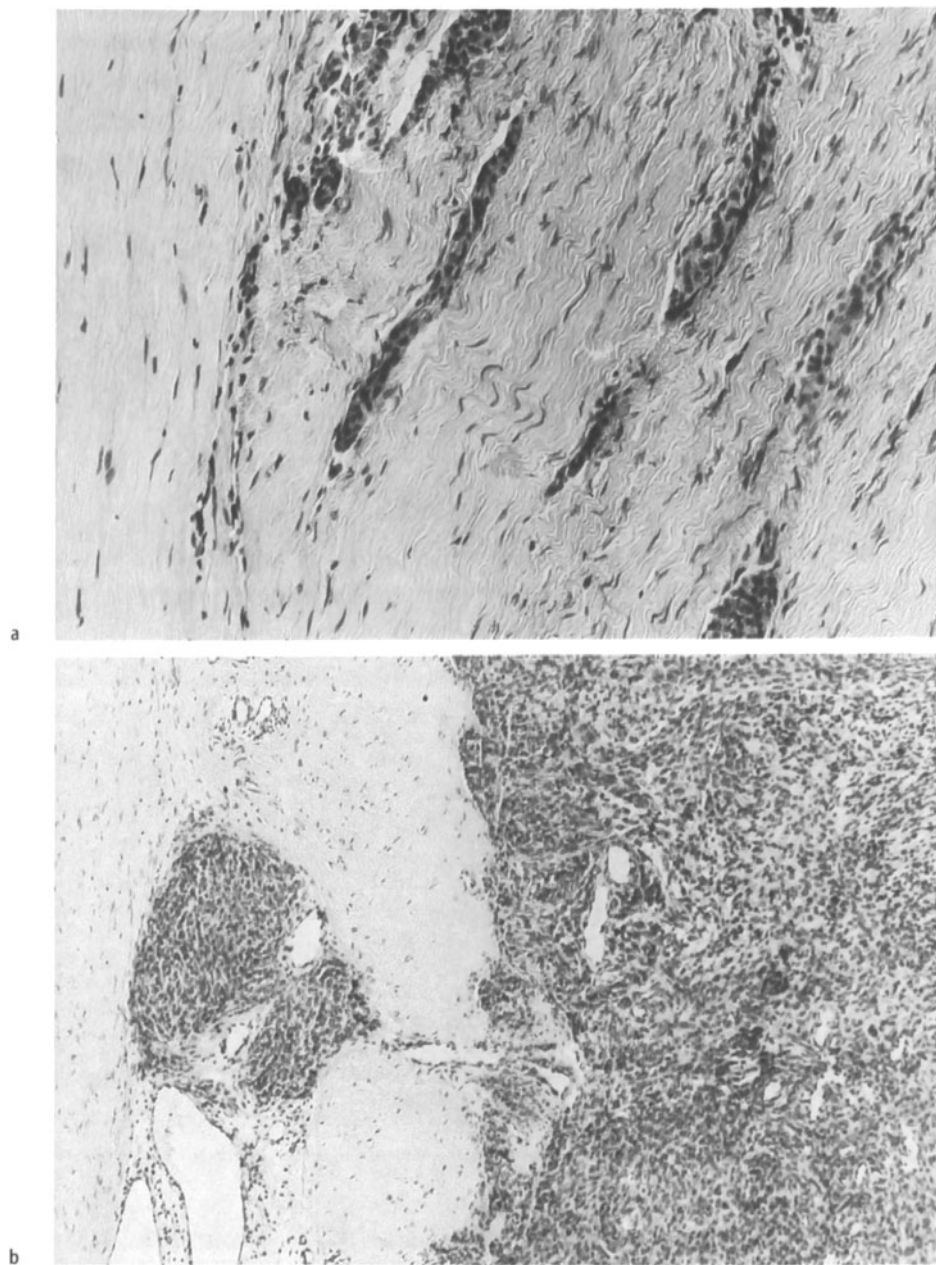
The *in vitro* culture of meningiomas has improved the differential diagnosis, for example, between certain neurinomas and fibroblastic meningiomas [1666] or between angiomatous meningiomas and angioblastomas [2347].

Polyamines, such as aminoguanidine, spermidine, and putrescein, induce variations in the growth velocity in relation to concentration, in particular morphological changes, usually represented by atypical cell features and multinucleated cells [782]. The formation of giant cells may increase following repeated subculturing and, therefore, has a degenerative significance [1618].

### 18.1.19

#### Growth Modality

Meningiomas are usually benign tumors, and their tendency to metastasize is considered to be an exceptional event. On the other hand, recurrences are fairly frequent, even though they can often be related to incomplete surgical removal or to a multicentric tumor growth pattern [2340]. In the great majority of cases, the tumors are capsulated and delimited from the surrounding tissue. The tendency to infiltrate is



**Fig. 18.21a–c.** Meningioma. **a** Tumor growth along fibers in the dura. H&E,  $\times 300$ . **b** Dural satellite growth. H&E,  $\times 200$ . **c** Malignant meningioma, MIB-1-positive nuclei. PAP-DAB,  $\times 400$ . (From [2992a])

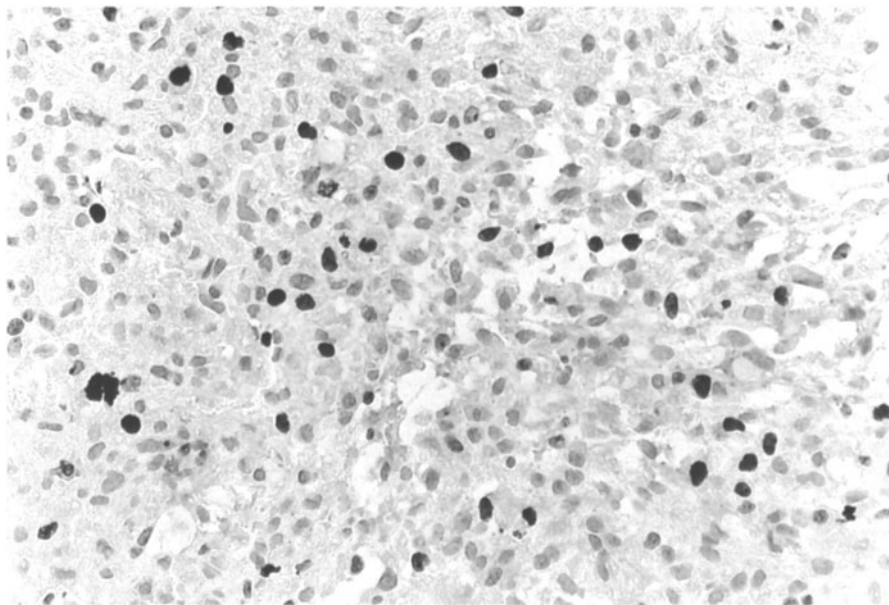


Fig. 18.21 (*continued*). c Legend see p. 378

usually limited to tissues of mesenchymal origin, such as the dura, venous sinuses, periosteum, bone and even pericranial muscle, but it is always a local phenomenon (Fig. 18.21a,b).

Bone abnormalities are frequently encountered in meningiomas, but they are difficult to appreciate. The most common occurrence is hyperostosis or endostosis, followed by bone destruction. Hyperostosing “en plaque” meningiomas are characterized by invasion of the haversian canals by meningioma cells, which stimulate the hyperostotic response. This condition is typical of women, and of the sphenoid bone. It implies surgical problems in removal. Calvarial hyperostosing “en plaque” meningiomas follow in frequency. Apart from these conditions, there may be bone destruction, more frequent at the base of the skull, hyperostosis by the invasion of a subjacent tumor, and endostosis. Also, intradiploic meningiomas have been reported [713].

The problem of malignant meningioma has already been dealt with. Some considerations regarding the cell kinetics, independent of malignancy, should be added. By the *in vivo* administration of bromodeoxyuridine (BrdU), it has been shown that the labeling index (LI) reaches not inconsiderable levels, and that in malignant recurrent meningiomas, it is much higher compared with classical recurrent meningiomas (Fig. 18.21c) [1411, 992]. The LI allows evaluation of the doubling time of the tumor and is correlated with the growth of the tumor as seen on CT scan [498]. Using the monoclonal antibody Ki-67 it has been observed that in recurrences and in anaplastic tumors the LI reaches 20%, while in classical meningiomas it is 1%. [2817]. Using flow cytometry, the biologically malignant behavior has been found to correlate with aneuploidy [1470] and with a high proliferative index obtained from the percentage

of cells in S and G<sub>2</sub>/M phase [2185]. These studies tend to demonstrate the predictability of the malignant behavior and of recurrence, not obtainable with the observation of the common histological signs indicating malignancy, including mitoses, which may be absent. The mitotic index (MI) has gross limitations [818], being of value only if positive: In many tumors, which later recurred, with a high proliferative index by flow cytometry mitoses were absent [2185]. Regional variations do not appear to play a role in these evaluations [1470].

#### 18.1.20

##### Metastasis

Metastases via the cerebrospinal fluid (CSF) are extremely rare, considering the frequency of meningiomas: In a review of the literature, 12 cases have been found [1642], nine of which showed histological signs of malignancy. In some rare cases, it was a benign, nonoperated tumor [2904]. Sporadic cases have been reported [1714, 1479]. A case of malignant intraventricular meningioma with metastasis via the CSF to the spinal cord has also been reported [1580].

Extraneural metastases are also rare, no more than 85 cases having been described up to 1982 [1642]; however, another 13 cases were found, and perhaps many have not even been reported [2904]. In a recent review, about 113 were listed, mainly in association with local recurrence [2927]. They are mostly tumors in adults, without any sex predilection, with some features of malignancy and predominantly of hemangiopericytic, papillary, or sarcomatous type. In many cases, they are histologically classical meningiomas [2799, 1792, 2268], and distant metastases are not synonymous with malignancy. The most affected organs are the lungs, followed by the liver, lymph nodes, bone, pleura, kidney, and pancreas [1642]. In general, these metastases occur in patients with recurrent reoperated tumors, sometimes even with characteristics of malignant transformation [1914].

#### 18.1.21

##### Prognosis, Treatment

Meningiomas are usually treated by complete surgical removal, which leads to total recovery. However, recurrences are common. Cushing [626] performed 522 operations on 282 patients. In the experience of Olivecrona [2493], recurrence appeared in 10% of parasagittal tumors, and according to Simpson [3201] in 21% of 332 meningiomas.

In general, the frequency of recurrences varies between 2.3% and 30% [1507, 2230, 3382]. These are meningiomas which at the first operation demonstrated benign histological features. In these cases, there may be at least two possible causes. On the one hand, it may be an incomplete surgical removal. In this case, the tumors presumably recur after a short interval, on average within 1–2 years [2669]; recurrences after a long time are, however, possible [880], given the slow growth of the tumor. There are numerous tumors, especially parasagittal, whose recurrences appear more likely to be related to arachnoid residues included in the dura or in the bone, and independent

of the previous tumor proliferation. In these cases, the interval has been calculated to be 5 years [3201]. These latter occurrences, therefore, seem related to the same cause which determines the frequent appearance of multiple meningiomas.

The histological examination of strips of dura taken from the base of attachment of meningiomas has demonstrated that they contain nodules or nests of clustered meningotheiomatous cells, which are not found in strips of dura taken from other pathological cases. These clusters may explain a number of recurrences [312]. They are called “grains of sand,” “nodules,” “clusters,” or “islets” of meningotheial cells responsible for recurrence [3691]. It remains to be clarified why these aggregates start to proliferate at a certain moment.

Histologically malignant tumors often recur; however, we still do not know which histological features are indicative of a poor prognosis. A partial answer to this question has already been given. As has been said, the frequency of recurrences seems to be closely correlated with an atypical or malignant histological appearance [1481, 1482].

Apart from studies finding more frequent recurrences of syncytial meningioma in comparison with the fibroblastic one, the histological features of poor prognostic value include mitoses, focal necroses, infiltration of neural tissue [600], and greater cell density [3214].

According to some authors, histological signs of anaplasia and typical and atypical mitoses are more indicative of a bad prognosis than necrosis and invasion of the nervous tissue [859, 3424]. For others, circumscribed necroses and bone infiltration are more frequent in recurrent meningiomas, whereas cortical invasion is not significant [517]. Micronecroses have been reconsidered as reliable prognostic indicators [2192].

One very important unanswered question is the definition of invasion of the nervous tissue, since histologically it greatly depends on observer evaluation. It is debated whether for invasion the tumor may just go beyond the Virchow–Robin spaces and arachnoid, without a layer of fibrous connective tissue between the tumor and the parenchyma, or whether the tumor has to reach the white matter or send prongs into the nervous tissue, where reactive astrocytes must be present. In general, it can be said that benign tumors recur in 3%–38% of cases and malignant tumors in 6%–78% [2927].

Malignant meningioma, identified on the minimal basis of high cell density and polymorphism, recurs in 44% of cases, as compared with 6% in classic meningioma [490]. Salcman [2927] demonstrated that benign tumors recur in 3%–38% of cases and malignant tumors in 41.6%–78%. The length of follow-up is very important in this evaluation [2631]. Today, special attention must be given to tumor necroses, because they could be the result of therapeutic preoperative embolization [2091, 2811].

Meningiomas usually grow slowly. In incidental meningiomas, discovered by CT, the annual growth rate has been calculated by repeated CT or MRI scans, and it was low [904].

A useful method for calculating the recurrence time may be that proposed by Cho et al. [498]: after administering BrdU to patients, the LI is compared with the doubling time as calculated on CT scans. The two parameters correlate, so the BrdU LI may be useful in predicting the tumor growth rate. In a recurrent tumor, with malignant transformation, the BrdU LI was found to be 9%, very high in comparison with 1% for classic meningiomas [1479].



The LI based on incorporation of [ $^3\text{H}$ ]thymidine or BrdU and on proliferation markers is of powerful predictive value. It has been observed that neither nuclear area nor nuclear content differentiate between classical and malignant meningiomas, but in the latter there is a significant increase in proliferation activity, as evaluated by the number of cells in S phase [2935]. The LI of BrdU administered *in vivo* was higher in recurrent tumors, whether malignant or benign [736]. It has been confirmed that BrdU LI correlates with recurrence rate [3165]. It is even possible to calculate the time to recurrence of completely resected tumors using the Shibuya formula:  $70.0 \times \text{LI} (\%)$  [3166]. Generally, histological features alone are not reliable for predicting the clinical course [2064].

In terms of predictive value, the nucleolar organizer region (AgNOR) count has also been considered [1820]. It is interesting to note that in other studies the AgNOR count distinguished between classical, atypical, and anaplastic tumors, but not between primary and recurrent tumors [2075].

Attempts to identify tumors with more aggressive clinical behavior have also been made using flow cytometric analysis [1470, 602, 2185] and Ki-67 [2817]. Proliferating cell nuclear antigen (PCNA) LI turned out to be a significant factor after univariate, but not multivariate analysis. However, together with mitoses it was predictive of outcome [1423].

Stereological analysis has also been used for prognostic purposes [2064].

Another prognostic factor identified in recurrences of intracranial meningiomas is the angioblastic variant [1525, 517, 12]. Moreover, recurrences are uncommon in very old patients, in spinal sites, and in fibroblastic tumors [136].

Radiotherapy of meningiomas is carried out occasionally for tumors in a special location or with a malignant histology or for repeated recurrences. It has been observed that the recurrence rate after radiotherapy diminishes from 74% to 29% [3609], and favorable results are sporadically reported in single cases or groups of cases [440]. The usefulness of radiotherapy in postsurgical treatment of meningiomas is a matter of debate. Some authors have found it helpful in incompletely resected benign tumors [2935, 2072]. It has not been ascertained whether this therapy is also of benefit in malignant tumors, because in these neoplasms radiation does not seem to prevent or retard tumor recurrence [2072].

Controlled observations do not seem to attribute positive effects to radiotherapy [1482]. Interstitial brachitherapy with radioactive iodine has also been efficaciously used in cases in which the surgical removal was difficult because of the location [1812].

## 18.2 Other Mesenchymal Tumors of the Meninges

### 18.2.1 Benign Neoplasms

Benign neoplasms are not frequent and include typical osteomas, chondromas, osteochondromas, lipomas, and fibrous histiocytomas. Fibrous histiocytomas, in particular, appear as solid, circumscribed masses composed of a mixture of fibroblasts, histiocytes, and lymphocytes with almost no mitotic activity.

## 18.2.2

### Malignant Neoplasms

#### 18.2.2.1

##### *Hemangiopericytoma*

This tumor, rich in blood vessels, was at first included by Cushing and Eisenhardt [629] among the angioblastic meningiomas. Since the first observations, an aggressive behavior of the tumor was recognized, and it was included with the hemangiopericytomas described in various parts of the body [186], being called meningeal hemangiopericytoma. The fundamental problem regarding this neoplasm is nosographic, i.e., whether it is a hemangiopericytoma developing in the meninges but similar to those in other parts of the body [186, 2668, 2607, 514, 1525] or a variety of angioblastic meningioma [2871, 1396]. Apart from the purely speculative interest of this debate [1642], some [2904] seem to be prone to consider it a variant of angioblastic meningioma, whereas others consider it to be a separate entity, not originating from arachnoidal cap cells [1528].

Different reasons have been given to keep this tumor separate from the meningioma group. Among the six put forward [400], the most important is that the tumor does not show any meningotheial characteristics. Transitional forms between hemangiopericytoma and meningioma exist [1642]. Though we have cases in our series, in our opinion this is not sufficient to deny it the dignity of a separate entity.

The frequency of hemangiopericytoma is not known with certainty; it varies from 2.4% [1201] to 4% [1525] and 7% of all meningeal tumors [1528].

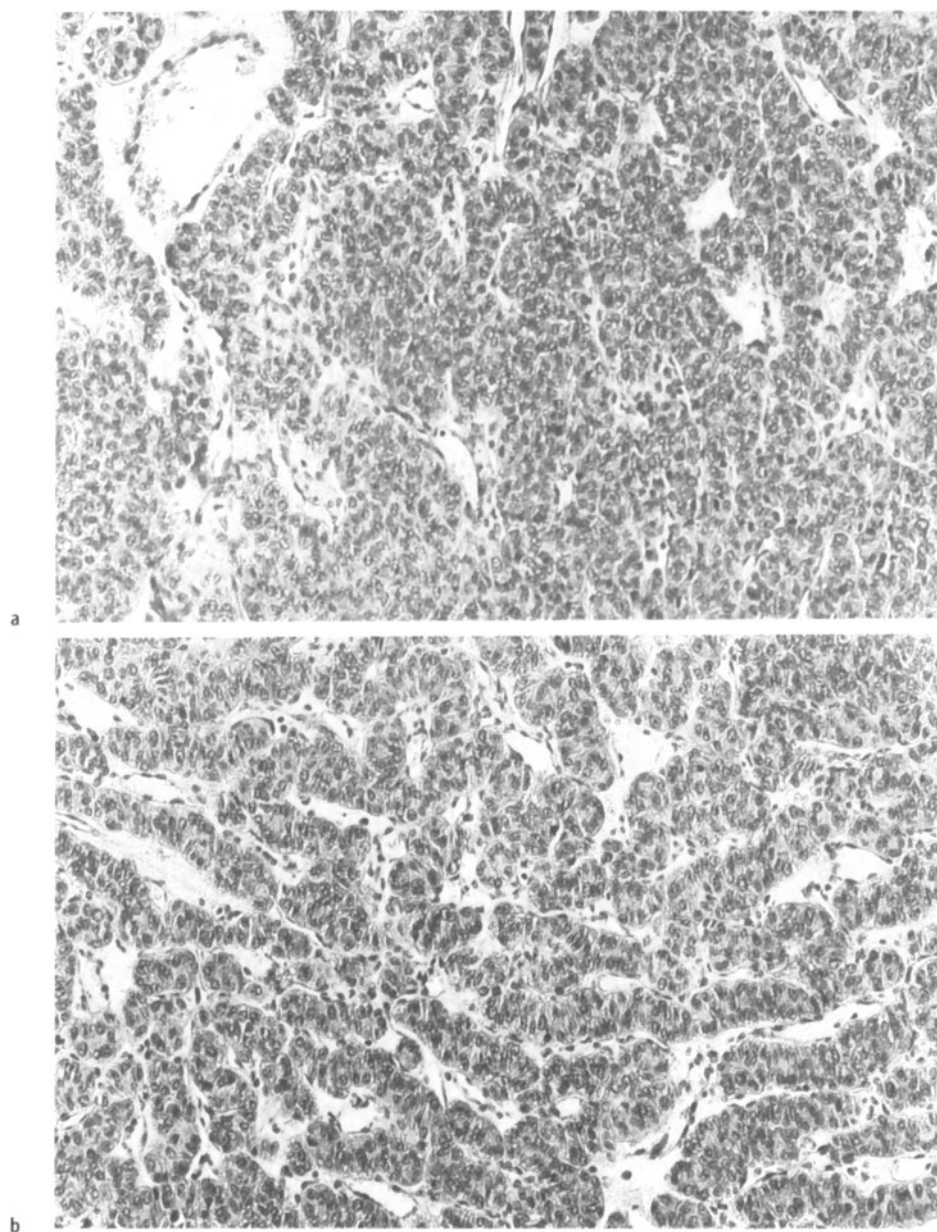
All ages may be affected, with a predilection for the fourth, fifth, and sixth decades, with no prevalence for sex, as in meningiomas. The locations of the tumor are those of meningiomas, with more frequent tentorial and subtentorial ones [1528].

The symptomatology does not differ from that of meningiomas and depends on the location of the tumor. Imaging is similar to that of meningiomas (perhaps the malignant ones), because of the frequent mushrooming. Enhancement with gadolinium does not provide better information.

The macroscopic aspect is that of a mass adherent to the dura, soft or consistent, with a smooth surface, and not capsulated. Usually, the tumor is highly vascularized.

Microscopically, the tumor is highly cellular. The cells are round or oval or irregular with a variable number of mitoses. There are many capillaries and small vessels with a slitlike lumen, lined by single endothelial cells (Fig. 18.22). The endothelium is separated by a basement membrane from masses of tumor cells which often abut on the lumen as a "cushion." Cells may also crowd into clusters. Tumor cells, supposed to be pericytes, are immersed in an abundant quantity of reticulin (Fig. 18.23). This is in continuity with the adventitia of blood vessels and forms a chaotic network. An interesting three-dimensional reconstruction study has been performed on vessels. Arteries abruptly divide into a large number of capillaries, and sinusoids show remarkable variations in caliber and bizarre indentations. The vascular structure can explain some angiographic characteristics of the tumor, such as the accumulation of contrast media and the prolonged circulation time [3572].

Under the electron microscope, the tumor cells show neither interdigitating processes nor the typical desmosomes of meningioma, whereas there is an abundant ex-



**Fig. 18.22a,b.** Hemangiopericytoma. **a** Slit-like vessel lumina. **b** Cordonal aspect. H&E,  $\times 200$

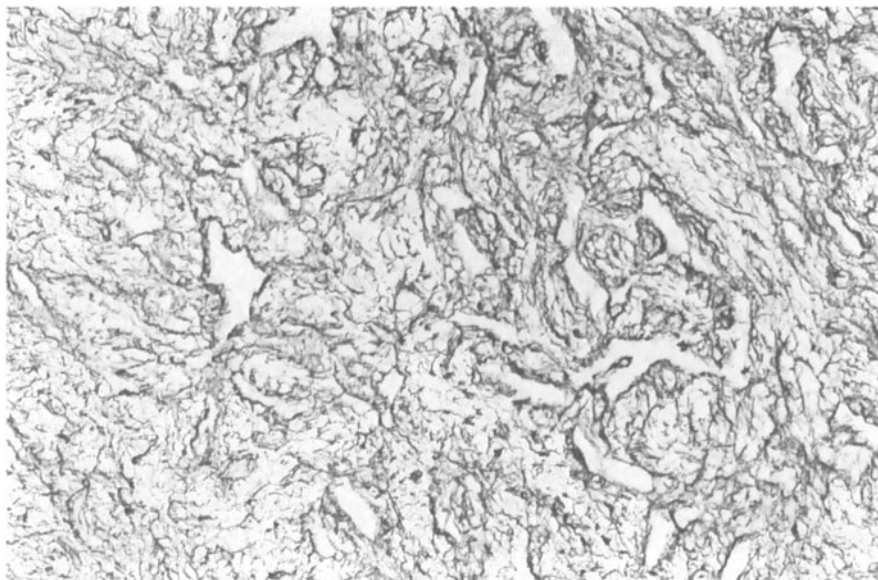


Fig. 18.23. Hemangiopericytoma, typical reticulin network. Gomori,  $\times 200$

tracellular, basal lamina-like material [646]. These features are important in differentiating this tumor from meningiomas. Attempts at whorl formation and intracytoplasmic filamentous condensations forming dense bodies similar to those of smooth muscle cells were seen [2607]. Both meningotheelial cells and pericytes may be present [472, 2281].

Immunohistochemical observations are rather inconsistent. On the one hand, there is evidence that vimentin and keratin are present in the arachnoid granulations, and in both meningiomas and meningeal hemangiopericytomas, contrary to the hemangiopericytomas of other parts of the body [1374]. This would confirm the meningiomatous nature of hemangiopericytoma. On the other hand, others have shown that both meningiomas and hemangiopericytomas are positive for vimentin and negative for EMA [1478, 3693].

Hemangiopericytoma has an aggressive behavior relative to the total group of meningiomas: Mean survival is 84 months in the former as compared with 100 in the latter [479]. Survival at 5 and 10 years was 67% and 40% [1201] compared with 83% and 77% [2280], respectively. It has high recurrence and metastasizing rates [3214], even years after operation. Local recurrences and metastases were 29 of 44 and ten of 44, respectively [1201].

They may also show a less aggressive behavior; thus, in the WHO classification, they may correspond to grade II and III.

Surgery is the treatment of choice, and it is attempted to remove the tumor completely. Adjuvant radiotherapy has been repeatedly carried out in this tumor, but the results are difficult to evaluate, because of the poor definition of the tumor and the inadequate number of cases. In a large series [1201], the free interval was overall better, changing from a mean value of 34–75 months. Doses higher than 45 Gy seem to

be more effective, without producing radionecrosis, which is rare after the irradiation of meningiomas [991]. The use of radiosurgery is currently being debated.

#### 18.2.2.2

##### *Fibrosarcoma*

Fibrosarcoma is the most common malignant meningeal tumor. Initially located in the craniospinal dura, it may subsequently extend into the dura itself, bone, leptomeninges, and neural parenchyma. In the 30 cases of Zülch (1956) [3799], there was no preferential location or predilection for age or sex. In another series of 25 cases [519], the average age was 29.5 years with nine cases in patients younger than 20 years.

Histologically, it is characterized by elongated cells, arranged in bundles in varying directions and forming reticulin and collagen. Histiocyte-like, pleomorphic, and lipidized giant cells may be present. The tumor must be differentiated from reactive, or even neoplastic, changes of the meninges secondary to invasion from malignant gliomas. Mitoses may be present in large numbers (Fig. 18.24). Necroses may occur. The cells are diffusely positive for vimentin and negative for desmin. Transitions have been shown between this tumor and malignant fibrous histiocytoma, with which it is often confused [1528].

Fibrosarcomas may also arise in the neural parenchyma, originating from the mesenchyme of the blood vessels, from perithelial cells, or from the meninges themselves. Histologically, they demonstrate the usual fibrosarcomatous features, including a tendency to nuclear polymorphism, numerous mitoses, and such differentiation phenomena as the formation of bone and cartilage. The differential diagnosis has to be made with gliosarcoma and giantocellular fibrosarcoma. Very important is the report of cases arising after radiotherapy [2448, 3605, 3087, 570, 2486].

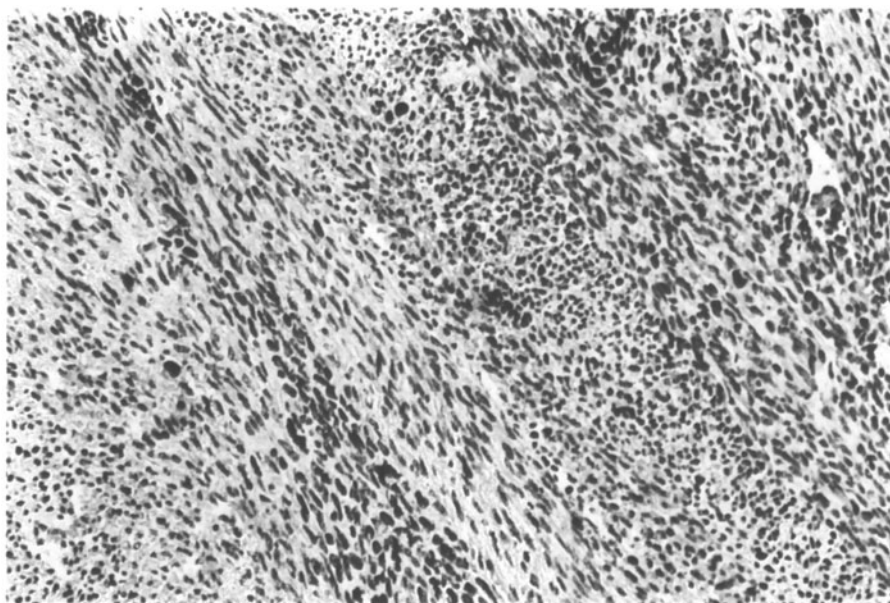
The tumor is very similar to or includes the mesenchymal component of gliosarcomas that have arisen after radiotherapy. According to the 1993 WHO classification, this tumor is categorized together with malignant fibrous histiocytoma (see Sect. 18.2.2.3 below).

#### 18.2.2.3

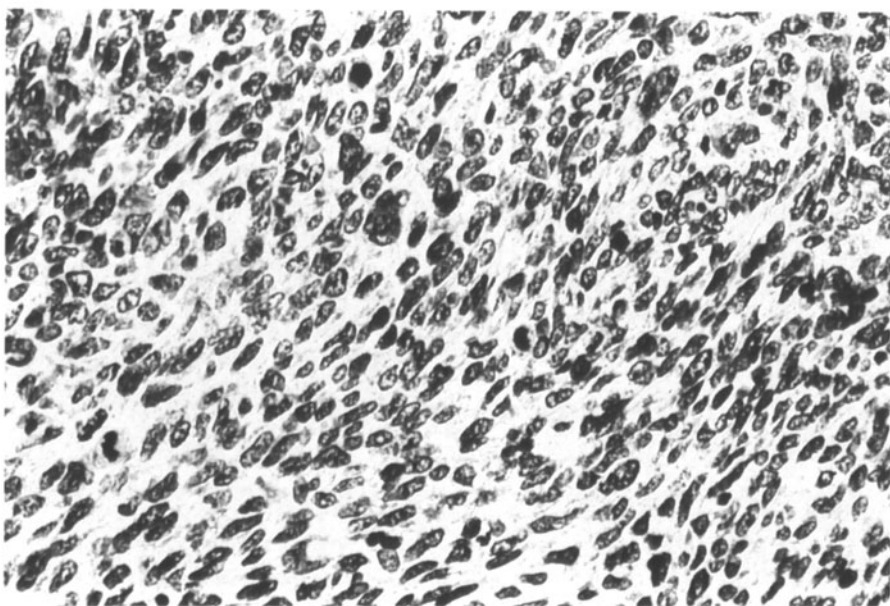
##### *Malignant Fibrous Histiocytoma*

These tumors appear as dural masses, either circumscribed or infiltrating adjacent structures. Histologically, it is a tumor of histiocytic origin with fibroblastic expression and showing a storiform pattern. The number of histiocytes and fibroblasts may vary, and often giant monstrous cells are present. A series of 20 cases has been reported [216].

The ultrastructural appearance is characterized by the two components [1243]; the histiocytic elements can be highlighted immunohistochemically with lysozyme and  $\alpha_1$ -antichymotrypsin [1682], even though the latter marker does not seem to be specific and monohistiocytic markers were negative or gave questionable results [2580, 2818].



a



b

Fig. 18.24a,b. Dural fibrosarcoma. a Bundles of elongated cells. H&E,  $\times 200$ . b Nuclear polymorphism and mitoses. H&E,  $\times 400$

The histological appearance is mostly that of elongated cells organized in bundles, pleomorphic, at times inflammatory, myxoid and angiomatoid [3639] or with giant cells (Fig. 18.25) [1528]. The tumor is glial fibrillary acidic protein (GFAP)-negative, apart from some reactive astrocytes.

The few cases of intracranial localization described thus far [1136, 1641, 1847, 1576] appeared connected to the meninges. Some intraparenchymal cases have also been reported [3202, 3194, 2826], one of which arisen after irradiation [1136]. A particular case in which the tumor arose 2.5 years after the removal of a mixed oligo-astrocytic tumor has been noted [2580]; it is probable that the causal event was the surgical trauma. The prognosis is very poor, with local recurrence and distant metastases [3194, 2584].

#### 18.2.2.4

##### *Primary Meningeal Sarcomatosis*

This is a diffuse sarcomatous infiltration of the meninges without a tumor mass, which occurs mostly in children [3419]. The lesion may spread around the spinal cord and may involve the brain. Histologically, it is composed of small, round or fusiform cells. The differential diagnosis includes extraneural sarcoma and lymphoma.

#### 18.2.2.5

##### *Primitive Melanoblastosis of the Leptomeninges*

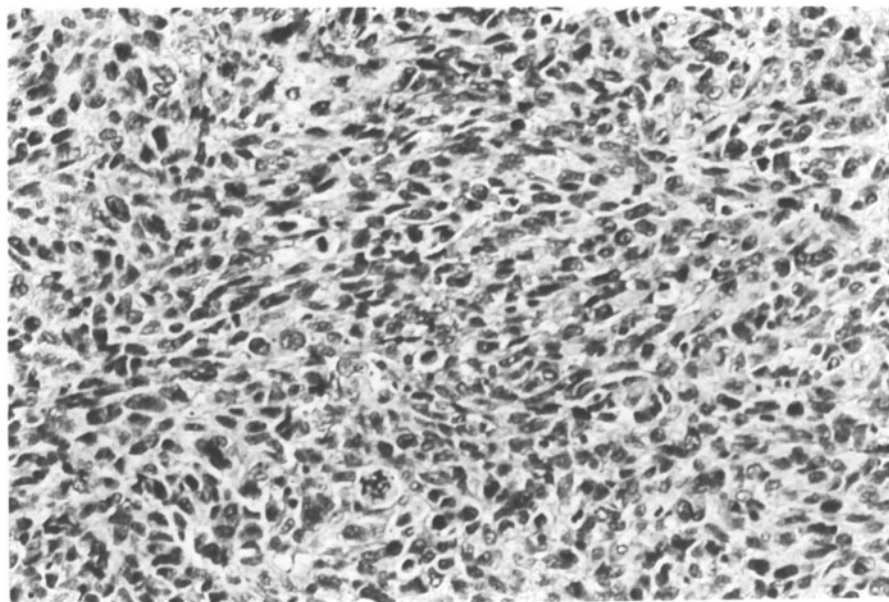
This is a rare condition, with fewer than 250 cases reported [2647, 377, 143]. In about 30% of cases, it is associated with hairy nevi of the skin. It is included in the group of neurocutaneous malformations [3500], and has no well defined clinical picture, and the prognosis is dismal. It can be identified in vivo only by cytological examination of the CSF.

The macroscopic appearance is characterized by cells containing pigment covering the meninges and filling the cisterns. This aspect is, however, variable, going from the discrete presence of pigmented cells to very aggressive tumors which may form tumoral masses.

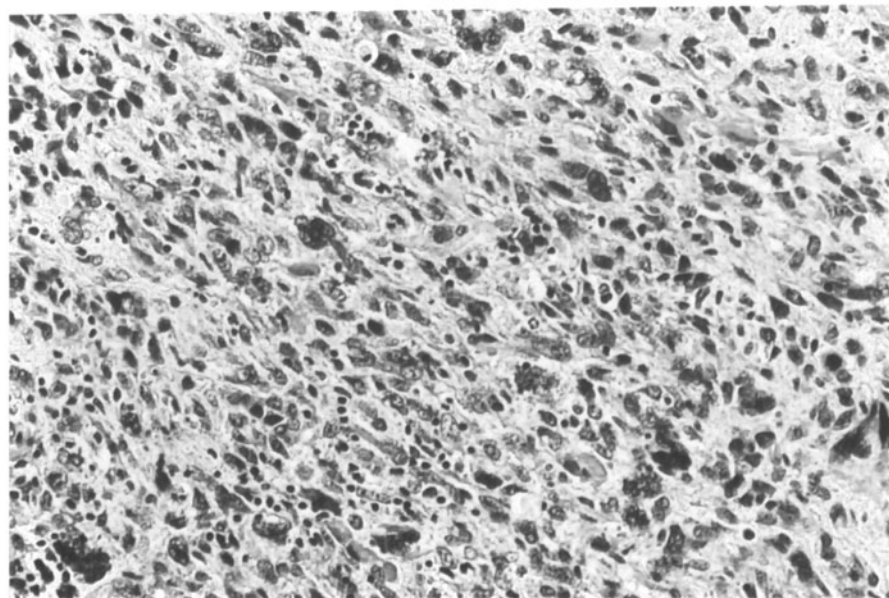
Microscopically, the cells have a round, polygonal, or elongated shape, and most contain melanin (Fig. 18.26). The nuclei may be polymorphous, but mitoses are not seen. Virchow–Robin cortical spaces may also be filled.

The pathogenesis of melanoblastosis has to be related to the hypothetical origin of the leptomeninges from the neural crest, to the definite origin of the pigmented cells from it, and to the presence of a certain number of melanocytes in the normal pia mater. The disease, therefore, belongs to the neuro-crestopathies, like von Recklinghausen's disease, Sturge–Weber disease, tuberous sclerosis, etc. It may present as melanosis or melanoblastosis, associated or not with growth centers and hairy nevi. In 63% of cases, it is represented by diffuse or multifocal melanoblastosis, in 37% by solitary pigmented tumors, and in 26% by melanosis or neurocutaneous melanoblastosis [143].

Disseminated melanomatosis principally concerns the meninges but may involve the cortex. The main problem in this disease is establishing whether it is a primary



a



b

**Fig. 18.25a,b.** Malignant fibrous histiocytoma. **a** Fibroblastic and histiocytic aspects. **b** Polymorphic aspect. H&E,  $\times 300$



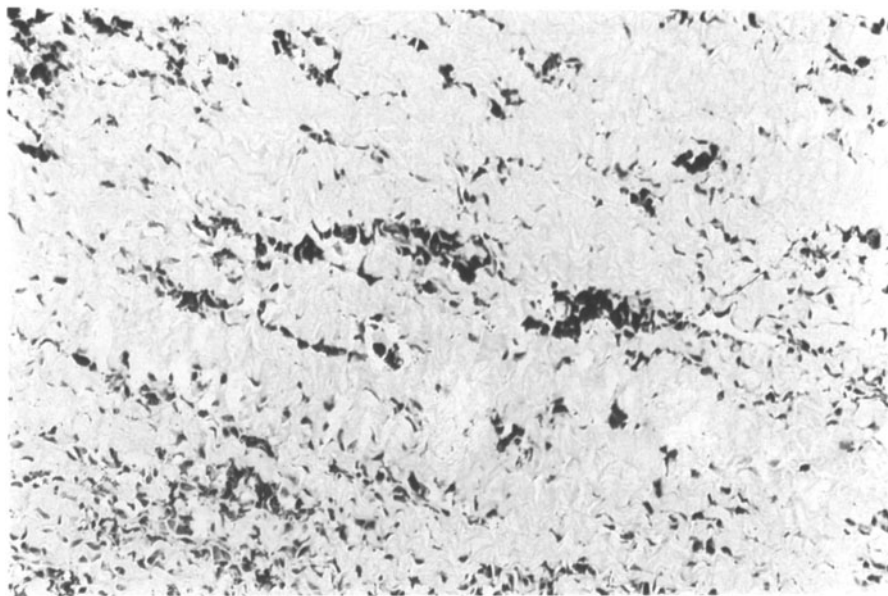


Fig. 18.26. Meningeal melanoblastosis. H&E,  $\times 200$

or a secondary form in which the primary tumor is not known. There are, in fact, cases in which the diffusion is such as to lead to the suspicion of a metastatic phenomenon, but the primary tumor cannot be demonstrated [1449]. It should not be forgotten that, after the lungs and liver, the brain is the preferential site for metastatic melanoma [2569]. In some cases focal melanotic masses may be found in the meninges or in the brain, with a preference for locations such as Meckel's cave. Their nature (primary or metastatic from a malignant melanoma) is very difficult to establish [3699].

The diagnosis of the disease is made by cytological examination of the CSF and is based on the demonstration of melanin, because the clinical symptoms are only poorly indicative or may generically indicate a carcinomatous meningitis [3434].

Radio- and chemotherapy are ineffective.

#### 18.2.2.6

##### *Primary Melanotic Lesions*

Primary melanotic lesions include circumscribed and nodular and diffuse lesions, varying from benign to malignant.

### 18.2.2.7

#### *Meningiomatosis or Meningoangiomatosis*

This is a rare, benign condition with meningiomatous and angiomatous hallmarks. Since it was first described [3720], no more than 17 cases have been reported; some others, after review, have then been reclassified differently. Recently, another case has been published [1965]. The condition may present clinically in two ways, either with epileptic fits and hemicrania in children or young subjects, or asymptomatic and found at autopsy in carriers of von Recklinghausen's disease. Intracranial calcifications visible on CT scan or abnormal blood vessels demonstrated at angiography are characteristic. Macroscopically, the meninges appear thickened and opaque, sometimes with the sulci filled by a granular material, especially in the temporal region.

Histologically, the thickened meninges show meningothelial proliferation, both diffuse and whorl forming, admixed with lymphocytes and macrophages. In the meninges, there are calcifications and sometimes fibrocartilage or bone. In the underlying cortex, there is a proliferation of small blood vessels surrounded by fibroblastic elements. The neurons are decreased in number. Sometimes there is gliosis, and Alzheimer's neurofibrillary tangles have been found.

In a recently described case [2581], there were "free fibroblasts" clustered in groups in the cortex, especially around blood vessels, immersed in protocollagen III and collagen IV and VI deposits, unlike perivascular cells which instead expressed protocollagen I.

It is distinguished from diffuse meningeal sarcomatosis because of the malignant character of the latter, the presence of cortical blood vessel proliferations, and the meningiomatosis.

Three pathogenetic theories have been put forward [1600]: an error in development; a cortical response to meningiomatous invasion; a vascular malformation followed by meningothelial proliferation. According to some authors [2581], the "free fibroblasts" are of meningothelial origin. It is probable that the proliferative perivascular response in the cortex can be attributed to these elements. In the study of a recent case was proposed that the lesion is a vascular malformation and that fibroblasts derive from vessel walls [1106].

A difficult problem is the presence of neurofibrillary degeneration. It has been supposed that the hydroxyapatite deposits responsible for the calcifications develop in neurons, thus interfering with the axonal transport of neurofilaments [1227]. This association has not been satisfactorily explained.

### 18.2.2.8

#### *Miscellaneous*

Other malignant mesenchymal tumors of the meninges are chondrosarcomas, liposarcomas, osteosarcomas, and mesenchymal chondrosarcoma.

## Mesenchymal Tumors

### 19.1

#### Chordomas

##### 19.1.1

##### General Considerations

The first description of these tumors was provided by Virchow [3554], who called them “*ecchordosis physaliphora*.” However, the chordal origin was suggested by Müller [2346], and the main hypothesis that the tumor arises from normal or aberrant residua of notochord [2777] was confirmed later [128] and is still widely accepted. The notochord, containing vesiculous embryonal tissue, appears at the fourth week of intrauterine (i.u.) life and progressively disappears in the seventh week. Its cephalic extremity is in close contact with the inner surface of the sphenoidal bone, in the region of the dorsum sellae, and extends along the midline over the pharyngeal surface of the developing occipital bone.

In the skull, nests of notochordal cells remain in the pharyngeal vault, the odontoid process, the spheno-occipital synchondrosis, and on the surface of clivus. In the vertebral column, these nests are found in the nuclei pulposi of the intervertebral discs, whereas in the sacrococcygeal region they are located laterally, ventrally, and dorsally. Chordomas may develop in all these sites.

Generally, a distinction is made between *ecchordosis physaliphora*, representing ectopic notochordal tissue, and true chordomas. The former is represented by small, asymptomatic nodules incidentally found at autopsy [3727, 3281] on the clivus, in the sacrococcygeal region, and, rarely, in the nasopharyngeal submucosal tissue or in the vertebral body [3486].

Chordomas can be classified topographically [1297] as tumors of the dens, clivus (spheno-occipital), hypophysis (sellar), occipit, sacrococcygeal, and vertebral regions. In relation to the developmental stage, they can be chondroblastic, chordoblastic in evolution, mature, and sarcomatoid. Mature forms are characterized by physaliferous and vacuolated cells and abundant intercellular mucoid substance, whereas sarcomatoid forms are characterized by anaplastic, giant, and monstrous cells. Immature, intermediate, and mature forms have also been distinguished [1016].

The frequency of chordomas is very low: 2% at autopsy [128] and 0.2% in pathological [3801] series. Until 1965 and up to 1979, 300 [1016] and 600 [3341] cases, respectively, had been published. It is likely, however, that many tumors escape detection.

The sites are those already indicated for notochordal nests. Half the cases are located in the sacrococcygeal region, 35% in the clivus and 15% are vertebral [935, 178, 1158].

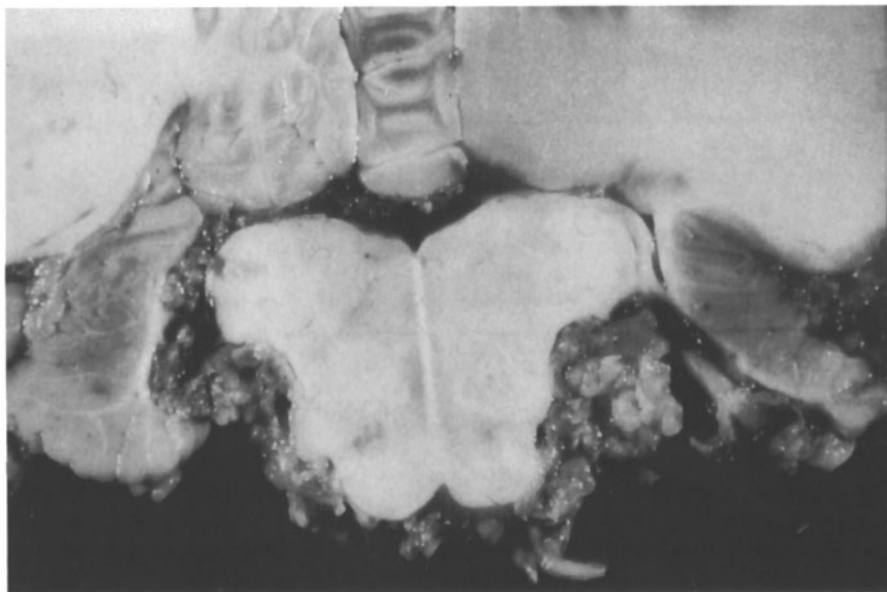


Fig. 19.1. Chordoma of the clivus

All ages are affected: cranial chordomas prevail in young people, and the sacrococcygeal tumors in the fifth and sixth decades. The difference, however, might be due to the earlier discovery of intracranial tumors. There is a male prevalence, especially for sacrococcygeal locations. It seems that trauma plays a pathological role, especially in sacrococcygeal locations, since the association is more frequent than sheer coincidence would indicate [3288]: notochordal cells may be displaced from their cartilaginous covering.

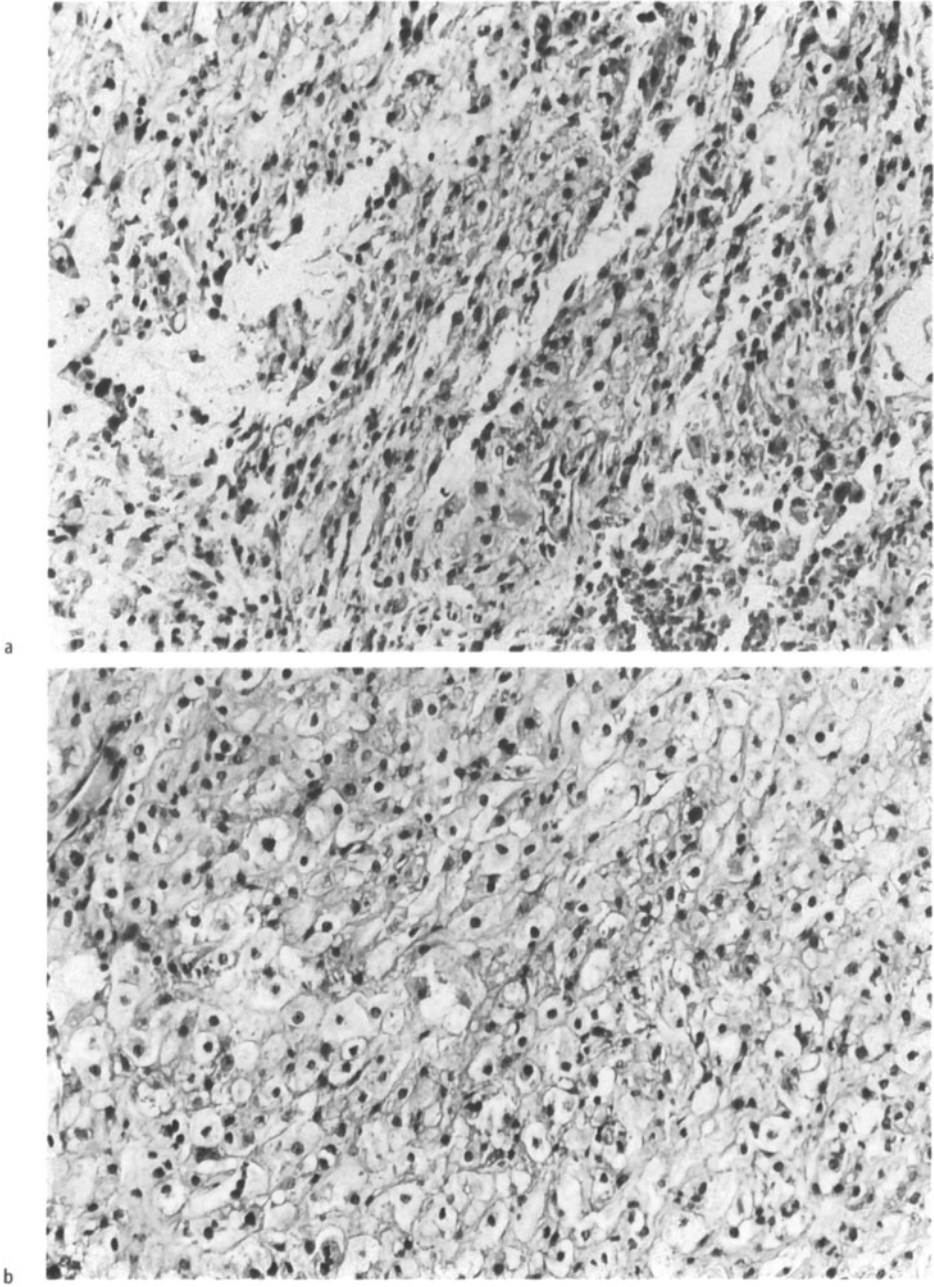
The clinical presentation depends on the location of the tumor. With computed tomography (CT), the tumor is isodense and destroys the bone, frequently with calcification; it shows varying contrast enhancement. On magnetic resonance imaging (MRI), the tumor is isointense and hyperintense on T1- and T2-weighted images, respectively. It cannot, however, be distinguished from chondrosarcoma. Angiography is performed, especially for a balloon occlusion.

### 19.1.2

#### Macroscopic Appearance

Ecchordosis physaliphora appears as small, circumscribed, gelatinous masses.

Chordomas are usually rounded, smooth or lobulated, whitish or yellowish, and gelatinous. The size may reach that of a nut. From the skull base, tumors may invade the interpeduncular cistern, sphenoidal cavity, and nasopharyngeal spaces. Those of the clivus (Fig. 19.1) may reach the foramen magnum and posterior clinoids. All the cranial fossae may be invaded by the tumor, which may erode the sphenoid, ethmoid,



**Fig. 19.2a–c.** Chordoma. **a** Elongated cell, chordoblasts. H&E,  $\times 300$ . **b** Typical physaliphorous cells. H&E,  $\times 300$ . **c** Cytokeratin-positive cells. PAP-DAB.  $\times 400$

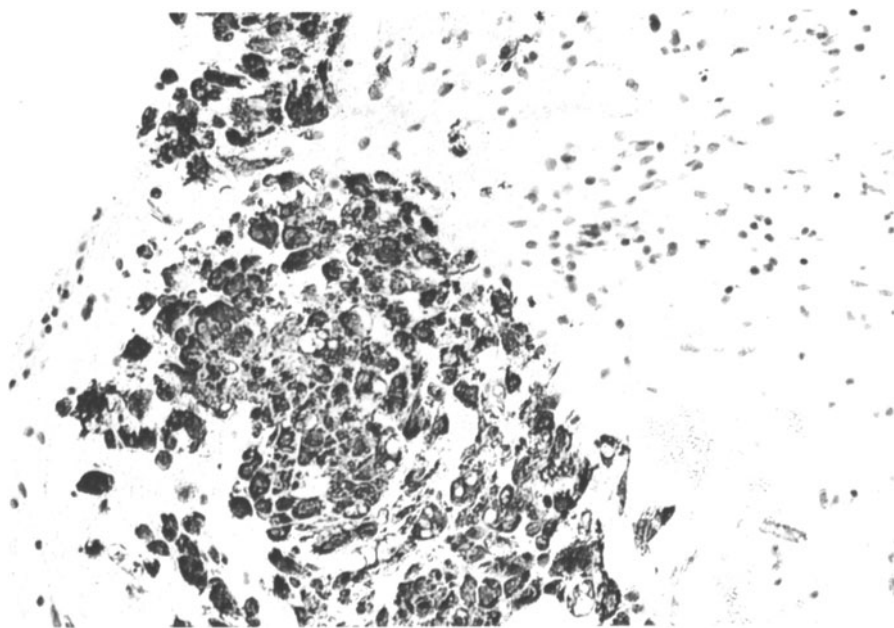


Fig. 19.2 (continued). c Legend see p. 394

and petrous bones with the orbit. Nervous structures are usually compressed but not invaded.

Vertebral tumors destroy vertebral bodies and also laminae and transverse and spinous apophyses. Sometimes the tumor may grow in the adjacent soft tissues, such as the laterocervical region, mediastinum, and pelvis. The spinal cord may be compressed.

Sacrococcygeal tumors may be divided into pre-, retro-, and central-sacral ones. There is always accompanying bone destruction.

### 19.1.3

#### Microscopic Appearance

Ecchordosis physaliphora is composed of vacuolated cells with a peripheral nucleus, often containing inclusions. The vacuoles may be empty or filled with metachromatic, periodic acid-Schiff (PAS)-positive, and alcianophilic material. The electron microscope reveals many affinities with chordomas [1347].

In chordomas, the aspect is that of notochordal tissue. The cells are disposed in bands or islands, with a mosaic-like or a honeycomb pattern, often around vessels [3124] or in a gland-like pattern [1016].

Round or elongated cells with eosinophilic cytoplasm and a hyperchromatic nucleus correspond to the chordoblasts of cytogenesis (Fig. 19.2a). Physaliphorous cells have a vacuolated or foamy cytoplasm with an eccentric nucleus which is poor in

chromatin (Fig. 19.2b). Still other cells are globular, with a small nucleus and an extremely vacuolated cytoplasm. These cells represent the most mature elements of the chordal series. The cell types are variably present in all the tumors, but according to the prevalence of a specific cell type, three forms of chordoma may be distinguished: immature forms, composed mainly of chordoblasts and rare, vacuolated, physaliphorous cells; evolutive forms, composed of cells in maturation and a mucoid, intercellular substance; mature forms which contain physaliphorous cells and large quantities of mucoid substance [3450]. Anaplastic forms are called sarcomatoid and contain atypical cells and rare mitoses [1016]. The intercellular substance is basophilic, metachromatic, and rich in glycogen.

The stroma is composed of reticular fibers dispersed among the tumor cells. Collagen bundles, sometime hyalinized, may be formed. Perivascular lymphocytic infiltrates may be present.

#### 19.1.4

##### Electron Microscopy

Under the electron microscope [970, 431], both elongated and physaliphorous cells are provided with long, ramified, and indented processes. The large vacuoles one sees are extracellular spaces delimited by the cell processes. In the cytoplasm of all cell types there are 75-Å thick fibers forming dense interlacing bundles. Smooth and granular endoplasmic reticulum (ER) may be abundant, and sometimes vacuolated. In the vacuoles there is a granular material similar to that of the extracellular “vacuoles.” Golgi apparatus are well represented, and mitochondria are abundant in areas without fibrils.

Intermediate filaments of 7–9 nm occur, of suspected tropocollagen nature, from which collagen is formed [3352]. They stain positively for keratin [13, 2258], which would suggest an epithelial nature, as suspected for the notochord itself [1631]. This hypothesis is confirmed by the occurrence of desmosome junctions in both chordomas and echordosis physaliphora [1347]. There are also linear subplasmalemmal densities, possible markers of a mesodermal mesenchymal nature [2282, 1347]. The double epithelial and mesodermal nature has already been attributed to the notochord itself [1232].

The study of the notochord in the rat demonstrated that the main difference from chordoma is the poorness of the extracellular spaces and the presence of mucoid material. The production of granular material, which corresponds to the mucoid substance, takes place in the distended ER [431, 843, 1055].

#### 19.1.5

##### Differential Diagnosis

The differential diagnosis has to include the newly introduced variant of “chondroid chordoma” [1281] and chondrosarcoma, because of their varied clinical courses. Chordomas are positive for cytokeratin [2717], epithelial membrane antigen (EMA), carcinoembryonic antigen (CEA), and also for tissue polypeptide antigen (TPA),

which is a marker of tumors derived from the epithelial lining of body cavities [396]. The testing of four epithelial markers on chordoma and chondromas demonstrated that the former are positive and the latter negative; chondroid chordomas behave like cartilaginous tumors. This means that either chondroid chordomas do not exist or they are “low-grade chondrosarcoma” [347].

### 19.1.6

#### Prognosis

There is no general agreement regarding the occurrence of distant metastases, which has been reported to vary from 5% to 43% [3341] and is more frequent for vertebral than for clivus tumors [1377, 3319]. Local recurrences are frequent, especially for sacrococcygeal tumors. They are due to incomplete removal rather than to malignancy, because only rarely can chordomas be totally resected. There does not appear to be any correlation between the histological appearance and clinical course [3341], even though immature forms are believed to have a malignant behavior. Chordomas, however, must be considered malignant, with invasive growth and local recurrence.

Conventional postoperative radiotherapy does not improve survival time, but prolongs disease-free interval [933]. Postsurgical, fractionated proton irradiation for skull base chordomas, however, repeatedly gave an 82% survival rate at 5 years [112]. Radiosurgical treatment is now being proposed [1745].

## 19.2

### Chondroma

Under this term are included all the tumors composed of differentiated cartilaginous tissue. Classically, those of the convexity and cranial base are kept separate from the spinal ones. Until 1961, there were in the literature no more than 42 operated or autopsied intracranial chondromas reported [2725]. However, by 1962 there were 50 [95] or 60 [1056]. In Zülch's published series, there are 20 chondromas, corresponding to 0.3% of all brain tumors.

In agreement with the dysontogenetic interpretation, tumors are mostly located at the skull base, where bone is formed upon the cartilage. The bones of the convexity, where these tumors are rarer, are formed, on the contrary, through a direct ossification of connective tissue. Two different pathogenetic theories are available for the two tumor locations: Convexity tumors could originate by metaplasia and be akin to meningiomas [629], while tumors of the skull base are more likely of dysembryogenetic origin and more akin to tumors at the same location, such as osteomas, lipomas, and fibromas, to which they may be related [1056].

Chondromas may be solitary tumors or belong to multiple chondromatosis (or Ollier's disease) or to Maffucci's syndrome, in which there is an association with subcutaneous hemangiomas [3454].

Chondromas of the skull base, initially located outside the dura and small in size, subsequently penetrate the cranial cavity. They are more common in females. An interesting case in a retrosellar location was reported [3543]. Convexity chondromas



are more common in the frontoparietal and parasagittal areas. They frequently originate from the convexity meninges, but sometimes from the falx, may reach a large size, and unlike those from the skull base, are more common in men.

Macroscopically, the tumors are whitish, smooth or lobulated, and hard-elastic in consistency.

Microscopically, they are composed of typical mature cartilage tissue, hyaline, fibrous, or elastic. In comparison with normal cartilage, they show slight morphological and structural anomalies, e.g., an uneven distribution of chondrocytes, morphological changes of isogenous groups, abnormal staining of the ground substance (Fig. 19.3a). Frequently, regressive phenomena such as vacuolar and mucous degeneration, hemorrhages, calcification, and ossification occur.

Chondromas are benign tumors, even though they are often difficult to treat surgically, especially those of the skull base. In rare cases, a malignant transformation has been reported.

### 19.3

#### Chondrosarcomas

Today, chondrosarcomas are accepted as a tumor entity and usually described as “central” and “peripheral” [1956], or “primitive” and “secondary” [1054], depending on whether they originate from normal cartilage or from a chondroma. In two rare cases, there was an association between a secondary spinal chondrosarcoma and an hereditary multiple exostosis [608].

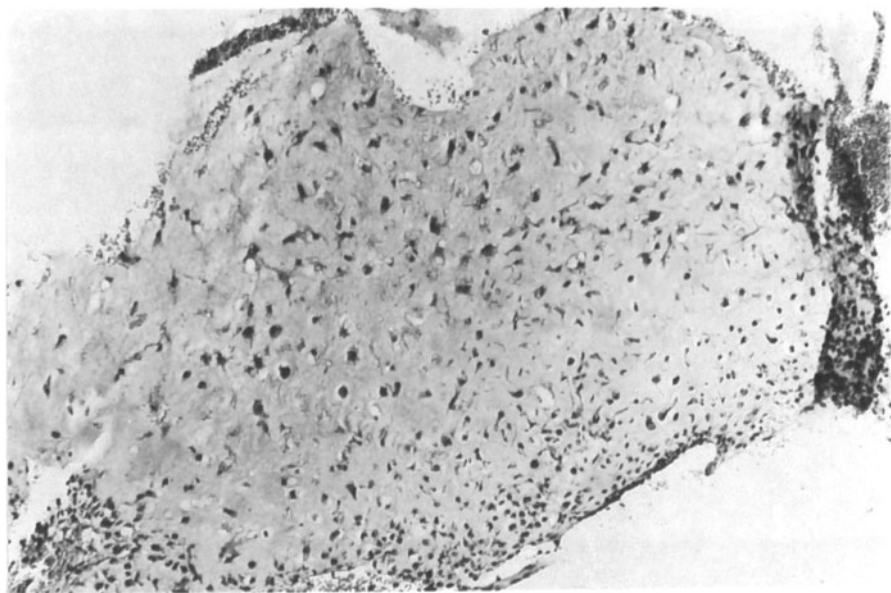
Chondrosarcomas represent 7% of the primitive malignant tumors of bone [642], but they are very rare among craniospinal tumors. A location at the skull base [1297, 95] is more frequent than that in the vertebral column [3322, 608]. Patients in the third and fourth decades are most often affected, even though “primitive” tumors seem more frequent in young subjects [551, 1956]. There is no difference between the sexes.

Macroscopically, they resemble chondromas with more pronounced cystic or hemorrhagic aspects.

Microscopically, all the stages of cartilage development may be observed, from that of embryonal mesenchyma to adult cartilage. Tumor cells are disposed in bands or trellises and form irregular, isogenic groups. There is nuclear pleomorphism with giant cells (Fig. 19.3b); mitoses are frequent and often atypical. There are intermingled fibrous, mucoid, and hyaline areas. The ground substance shows staining anomalies and is usually strongly basophilic and metachromatic.

Practically speaking, the myxoid, differentiated, and mesenchymal forms [2977] are to be distinguished. The last is characterized by bundles of undifferentiated cells with cartilage islands (Fig. 19.4). The cells are elongated. Immunohistochemistry testing with neuron-specific enolase (NSE) and anti-Leu-7 is of little help in the differentiation from neuroepithelial and other mesenchymal tumors [3351].

The tumor is malignant, with local recurrence and distant metastases.



a



b

**Fig. 19.3. a** Chondroma, distribution of chondrocytes. **b** Chondrosarcoma, anaplastic elements and necrosis. H&E,  $\times 300$

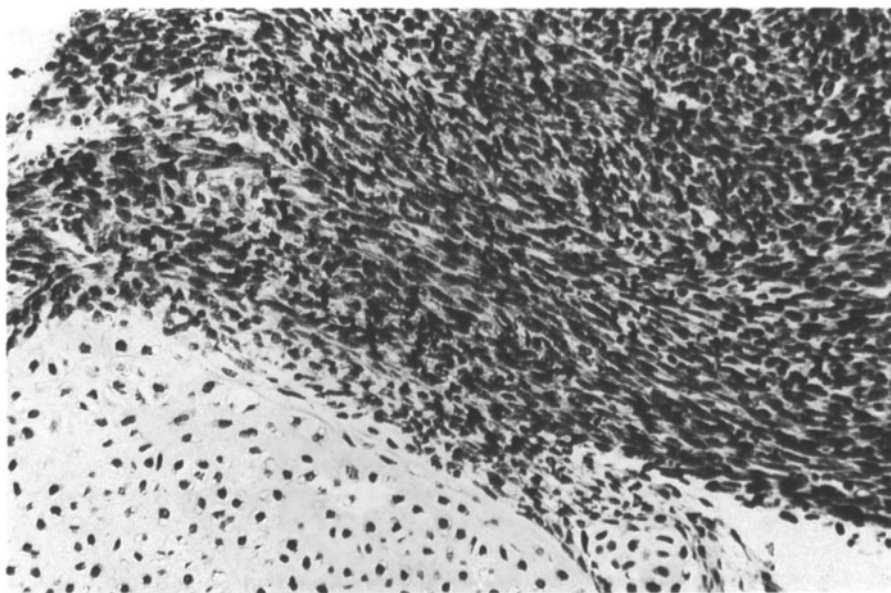


Fig. 19.4. Mesenchymal chondrosarcoma. H&E,  $\times 200$

## 19.4 Osteomas

These tumors usually grow very slowly. They can develop superficially, as small, single or multiple exostoses of the external or inner surfaces of the skull, convexity, or base, especially on the lesser wing of the sphenoid. Reports of an osteoma of the internal acoustic meatus [1297] and in the nervous parenchyma [229] are exceptional.

Two pathogenetic mechanisms have been considered, traumatic and dysembryogenic. Not infrequently have osteomas arisen at the site of trauma [788]. The dysembryogenic hypothesis is the same as for other tumors, i.e., an origin from included embryonal residua.

A compact osteoma, solitary and typical of the cranial bones, is distinguished from a spongy osteoma, typical of the long bones. An osteoid osteoma [1494] originates from the spongiosa, produces osteoid substance, and involves successively the cortical lamina and the periosteum. Another type is the “eburneal” osteoma of the paranasal cavities, which may involve the frontal and ethmoidal sinuses and the orbit [626].

Histologically, osteoma is composed of lamellar bone tissue with few haversian canals, similar to the compacta of normal bone. Spongy osteoma is similar to the spongiosa. Sometimes, vessels are abundant and of angiomatous aspect.

All osteomas are benign tumors, but sometimes they reach large dimensions and represent real surgical problems: a personal case weighed 444 g. They appear in a wide range of ages (3–67 years in a personal series), and there is a prevalence among females.

## 19.5

### Osteosarcoma

Osteosarcomas are rare tumors, mainly localized in the limbs, but exceptionally also in the skull, and have a slight prevalence for young subjects and men. An origin from the meninges [1848] or from the nervous structures is very rare [1507].

Macroscopically, the tumors are irregular in shape, gray-reddish, and of variable consistency. Sometimes, the tumor is soft because of regressive events and sometimes hard because of bone neoformation. The infiltrative growth is clearly evident.

Osteosarcomas are malignant with extensive invasiveness, and produce distant metastases.

## Vascular Tumors

### 20.1

#### Capillary Hemangioblastoma

Hemangioblastoma (Lindau's tumor) is a neoplasm which is found mainly in the cerebellum and is characterized by the progressive growth of angioblastic elements. When associated with carcinoma, vascular tumors, or benign cysts of eyes, kidneys, pancreas, or adrenal glands, paraganglia, or epididymis, it forms the von Hippel-Lindau's (VHL) syndrome [1966, 1905]. The association is fairly rare [2494, 2406, 3592]. However, after the recent cloning of VHL gene [1879] and the modification of the minimal criteria for VHL diagnosis [2405], each patient with a cerebellar hemangioblastoma is a candidate for VHL diagnosis. The discovery of the genetic basis of the disease casts doubt on the previous dysembryogenetic hamartoblastomatous pathogenetic theory [3592, 628, 3295] (see also Sect. 22.3).

Syringomyelia may be associated with spinal hemangioblastomas.

Cushing and Bailey [628] were among the first to suggest an origin of hemangioblastomas from aberrant vascular germs. Such an interpretation applies for the most common location, the cerebellum [3295]. In fact, the intense proliferation and vascularization of the area postrema which occurs around the third month of fetal life may account for the possible inclusion of undifferentiated embryonal cells, such as angioblasts, which might subsequently develop a neoplastic potential for reasons still not understood.

#### 20.1.1

##### Biological Data

The frequency varies in the different series from 1.9% [628], 1.5% [1007, 3801], to 0.8% [2406] of all intracranial tumors. If posterior fossa tumors only are considered, their incidence rises to 7.3% [2494].

Some 83% of hemangioblastomas are located in the posterior fossa [2406]. Besides the cerebellar hemispheres, the vermis, fourth ventricle, and medulla (especially the area postrema) are preferred locations. Supratentorial and spinal cord examples have been described, but they are less frequent. Up to the end of 1978, 23 intracerebral cases had been reported [1895].

Extramedullary locations involving the spinal roots or cauda equina or even peripheral nerves are exceptional. Hemangioblastomas are usually isolated tumors, but occasionally may be multiple or in the cerebellum and spinal cord or in the cerebellum and cerebrum [862].

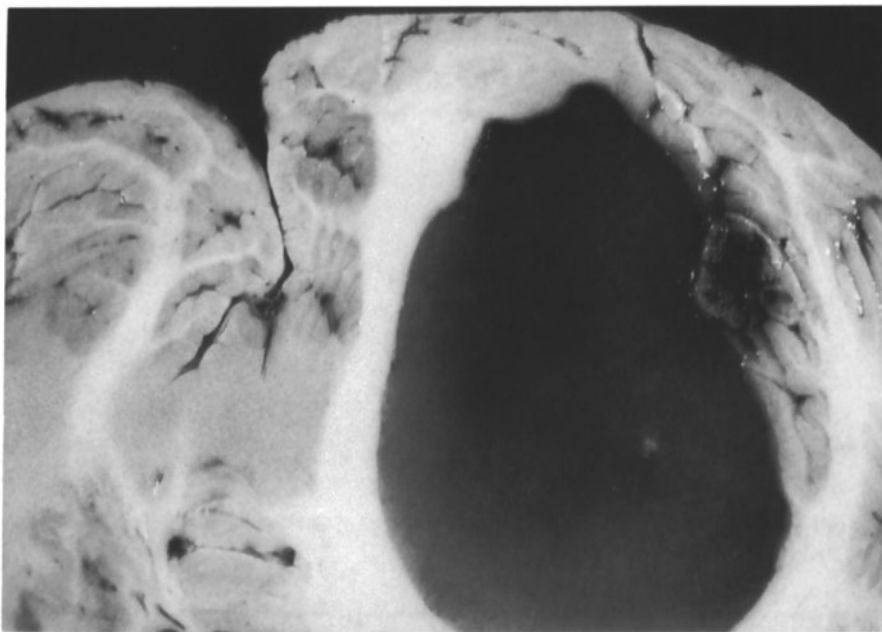


Fig. 20.1. Cerebellar hemangioblastoma, large cyst with a mural nodule

The majority of tumors are diagnosed between 35 and 45 years of age. Children are rarely affected [887]. When the tumor is part of VHL syndrome, the average age is lower (29 years) [2406].

Males are affected more frequently than females, but in some series, both sexes are equally represented [2406].

Clinical presentation depends on the location of the tumor. In posterior fossa, cerebellar signs, especially ataxia, dominate. On computed tomography (CT) scan, the tumor appears as lobulated masses, with the same density as cerebrospinal fluid (CSF). On magnetic resonance imaging (MRI), it shows prolonged values both on T1- and T2-weighted images.

### 20.1.2

#### Macroscopic Appearance

Hemangioblastomas are not encapsulated, mostly cystic tumors, of variable consistency, but generally hard-elastic, reddish-brown or reddish-blue, in colour and well circumscribed from the surrounding tissue. They are of variable dimension, from the size of a walnut to a mass replacing most of the cerebellar hemisphere. Cysts may be of various sizes and may be multiple, but usually there is a single large cyst which forms the main body of the tumor, the solid part being represented by a small mural nodule (Fig. 20.1). The cysts have a yellowish or brownish fluid content

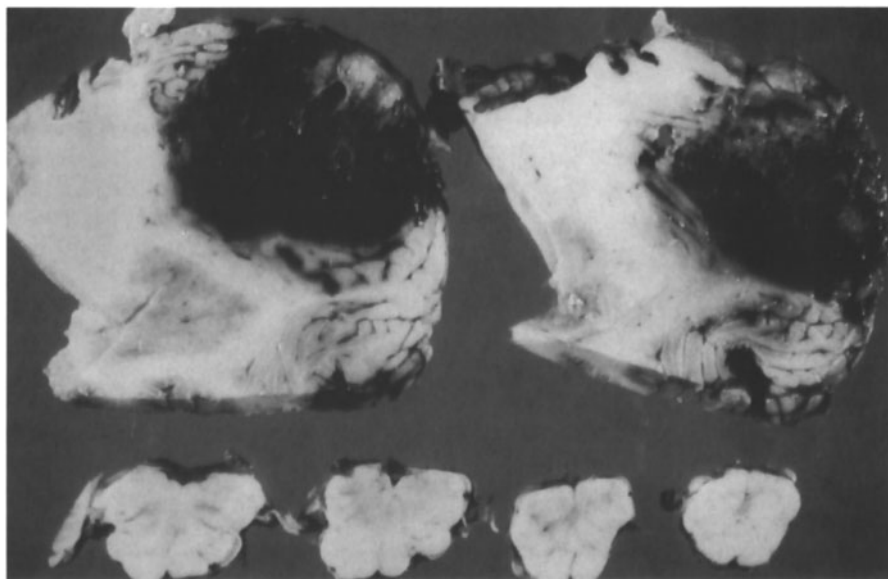


Fig. 20.2. Hemorrhagic cerebellar hemangioblastoma

which often coagulates spontaneously when it is exposed to air. The internal part of the cyst is smooth and whitish or rusty if intracystic hemorrhages occur (Fig. 20.2).

### 20.1.3

#### Microscopic Appearance

The main feature of the solid areas is the presence of a network of lacunae and newly formed blood vessels of different shapes, orientation, and caliber. Blood vessels vary from capillaries to sinusoidal or lacunar spaces (Fig. 20.3). Reticulin staining or methods demonstrating a basement membrane highlight the blood vessel network and the intervascular cells arranged in islands or in epithelial-like cords (Fig. 20.3b).

Blood vessels of the capillary type are formed by endothelial cells resting on a basement membrane in continuity with a rich argyrophilic intercapillary and interstitial network (Fig. 20.4a). There are also blood vessels showing various alterations in their walls, and vascular spaces having a cavernous appearance or forming sinusoids filled with blood. Their endothelial lining is often discontinuous and fenestrated, so that some segments of the lumen appear delimited only by elements of the surrounding interstitial stromal tissue.

The capillary endothelia differ from normal brain capillaries in that they contain many pinocytotic vesicles and fenestrations and Weibel-Palade bodies. The barrier function of the capillaries is absent, so that the tumor is considered “leaky” in neuroimaging terms [1362]. Immunohistochemically, endothelial cells show a high ex-

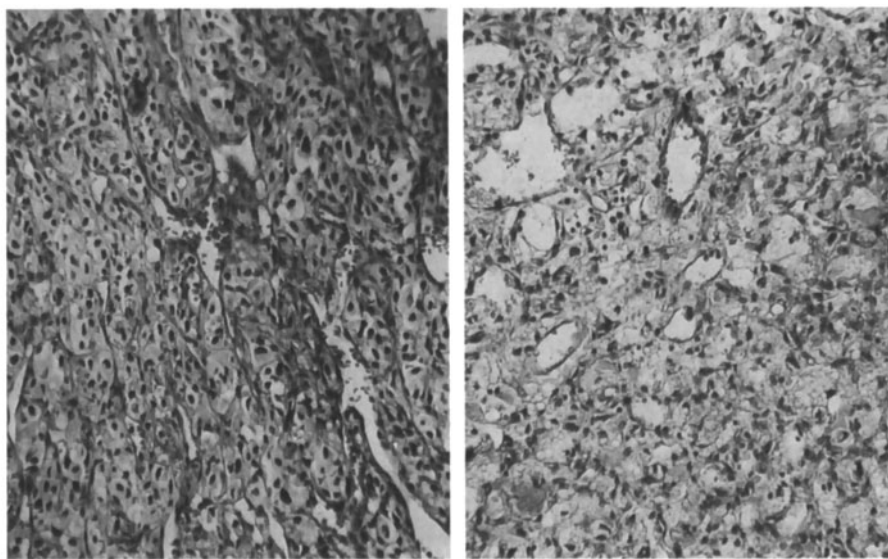


Fig. 20.3a,b. Cerebellar hemangioblastoma; many capillaries intermingled with intermediate cells, arranged in islands or cords. (From [2994]) H&E,  $\times 200$

pression of the Glut-1 glucose transporter isoform, in line with their leaky barrier characteristics [574].

The endothelial cells of the capillaries and lacunae are usually swollen, isomorphic, and with hyperchromatic nuclei. Stromal cells have an epithelioid appearance or are polyhedral, with clear, hypochromatic nuclei often containing a prominent nucleolus. In paraffin sections, their cytoplasm usually shows variable vacuolation up to the formation of a large single vacuole delimited by a plasma membrane (Fig. 20.4b). Frozen sections stained with Sudan black and examined under polarized light may demonstrate the presence of sudanophilic birefringent material. Not infrequently, however, lipids are absent, and the cytoplasm is pale, homogeneous, or finely granular. Fat droplets are easily seen under the electron microscope (Fig. 20.5). Because of their resemblance to the foamy cells seen in some dysmetabolic conditions, they were called by Lindau [1966] and Lozano and Costero [2031] “pseudoxanthomatous.”

The nuclei of this cell type are usually fairly uniform but sometimes show a discrete pleomorphism (Fig. 20.6). In some cases, giant uni- or multinucleated cells may be present. Mitotic figures are generally not present.

The nature of the interstitial cells has been discussed for a long time and remains controversial. In general, the prevailing idea is that they derive from the pia or have an angiogenic origin [691, 2201]. The problem is made more difficult by the frequent finding of glial fibrillary acidic protein (GFAP)-positive cells of astrocytic type in the tumors. These are generally considered as reactive astrocytes trapped in the tumor [1641, 691, 2201, 3018, 43]. Sometimes, polygonal GFAP-positive lipidized cells of stromal type without processes are present (Fig. 20.7). They are vimentin-positive also and may be reactive, lipidized astrocytes [1641] or stromal elements which have



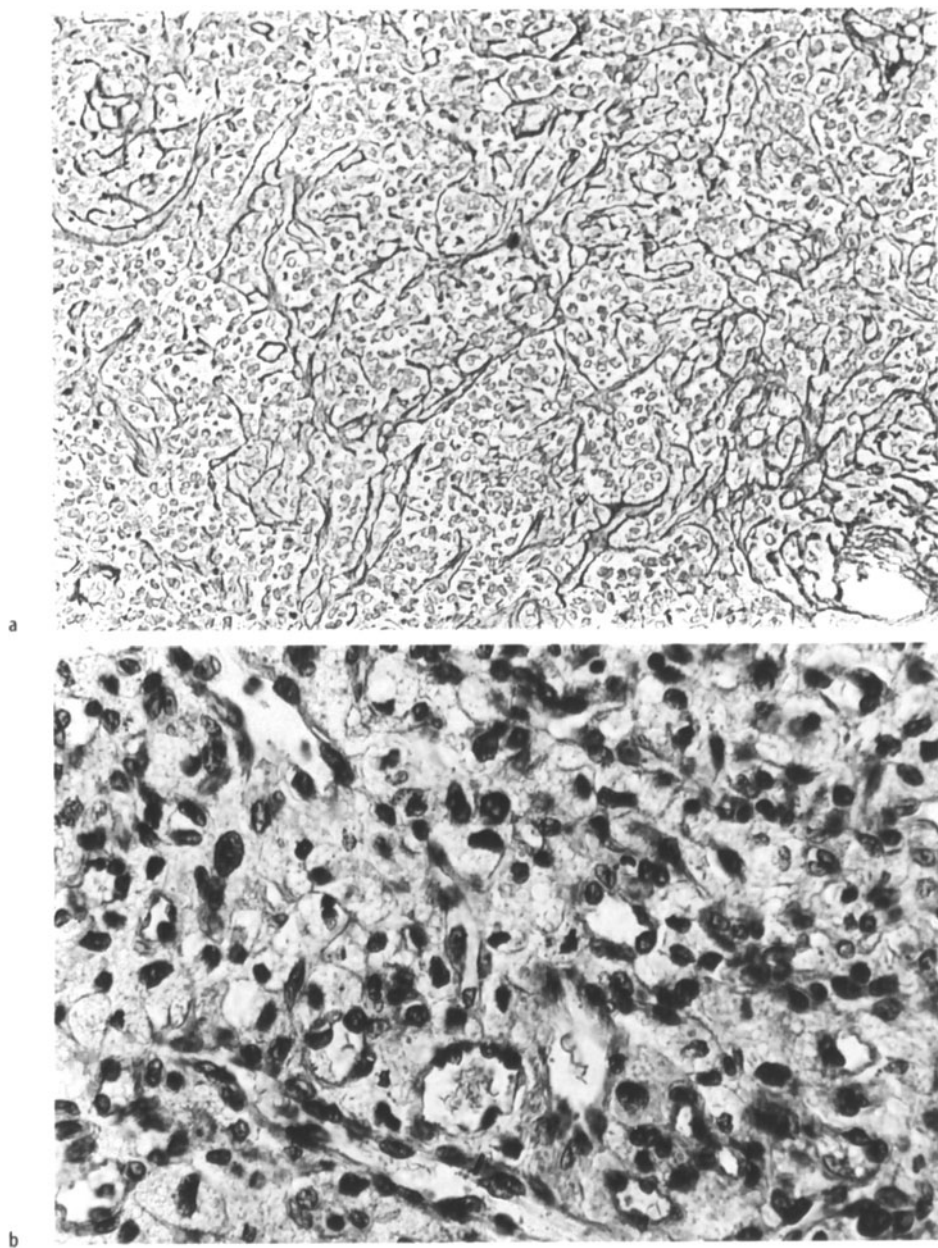


Fig. 20.4a,b. Cerebellar hemangioblastoma. **a** Rich argyrophilic network. Gomori,  $\times 200$ . **b** Intermediate cells with granulous and vacuolated cytoplasms. H&E,  $\times 400$

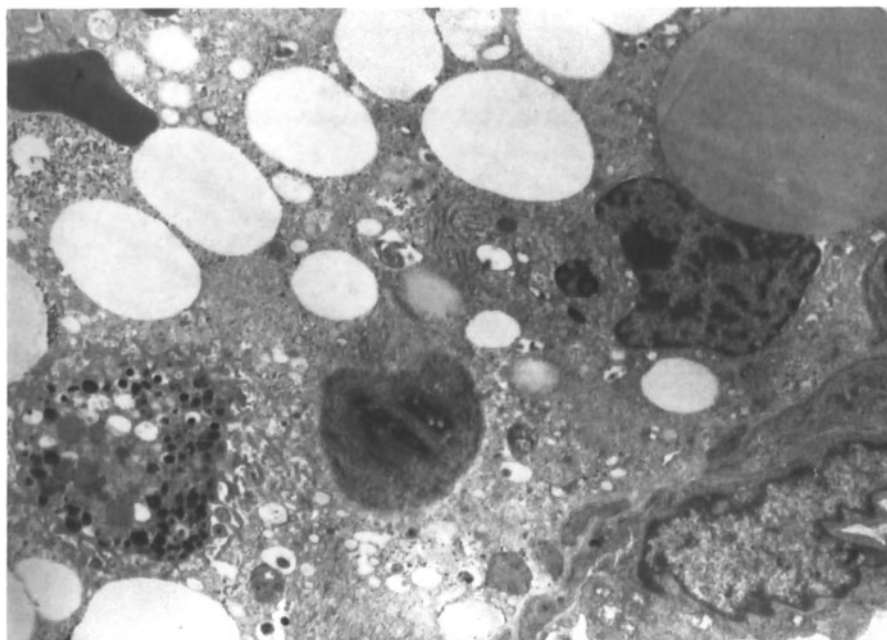


Fig. 20.5. Cerebellar hemangioblastoma, fat droplets in the cytoplasm of intermediate cells. Uranyl acetate, lead citrate stain,  $\times 4000$

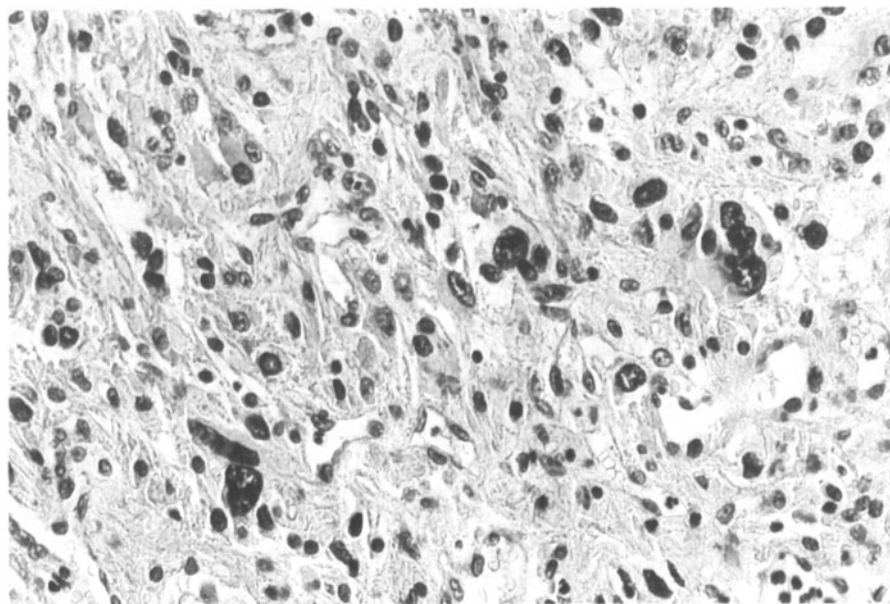
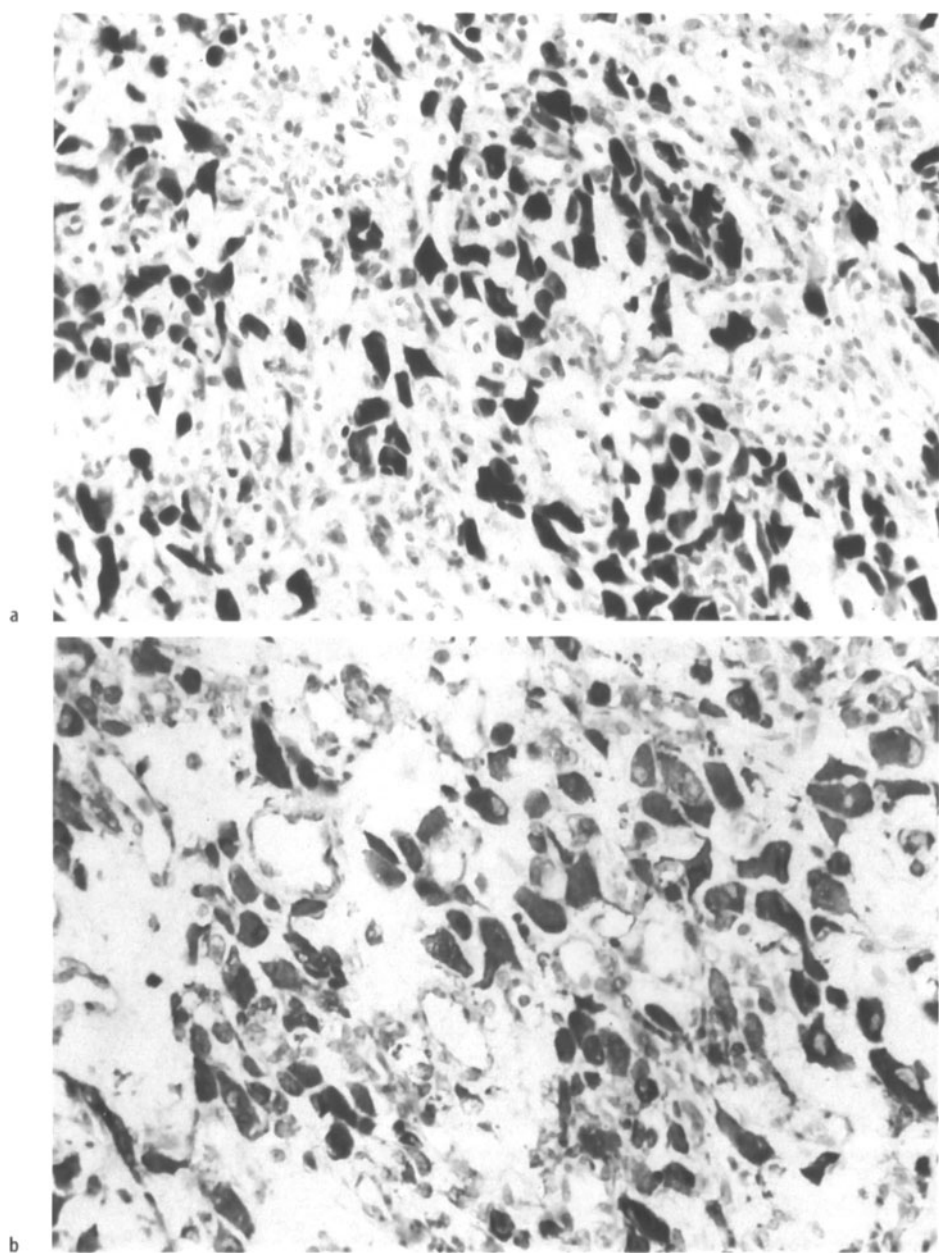


Fig. 20.6. Cerebellar hemangioblastoma, nuclear polymorphism. H&E,  $\times 400$



**Fig. 20.7a,b.** Cerebellar hemangioblastoma. **a** Glial fibrillary acidic protein (GFAP)-positive cells. **b** Vimentin-positive cells. PAP-DAB,  $\times 400$

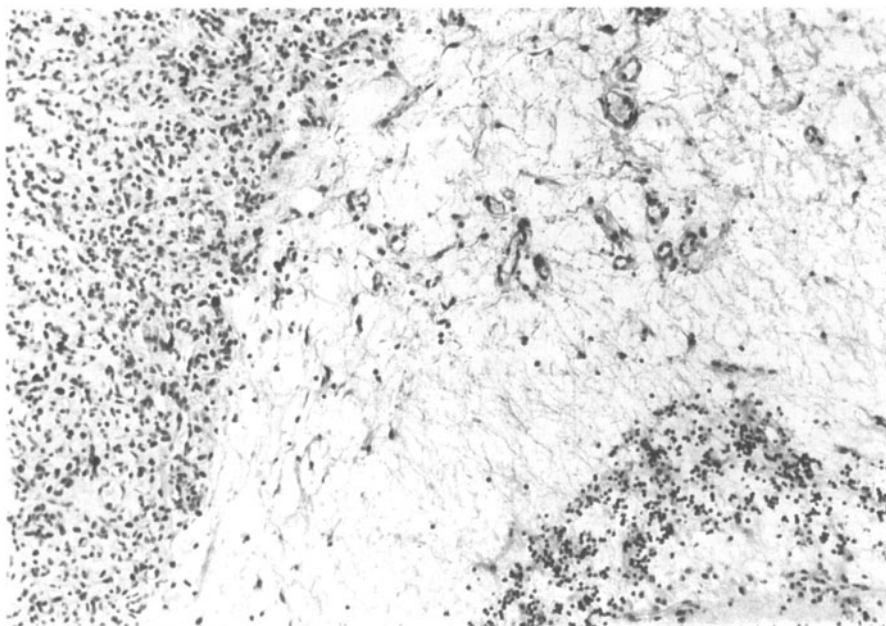


Fig. 20.8. Cerebellar hemangioblastoma, sharp limits of the tumor. H&E,  $\times 200$

taken up GFAP from the environment [691]. However, the astrocytic component may be somewhat conspicuous [2203], even though the aspect of a mixed glioma or angioglioma is never achieved [300].

On the basis of the main morphological features, cellular, capillary, and cavernous variants of hemangioblastoma are distinguished [628]. The former is characterized mainly by stromal cells, which are positive for vimentin [3022] and therefore hardly distinguishable from astrocytes. Their positivity for fibronectin [1732] permits, on the contrary, such distinction.

The tumor, as already noted, has no capsule, but it is constantly sharply delimited from the normal nervous tissue (Fig. 20.8). Its limit with healthy tissue is marked by the presence of masses of small blood vessels, and often there is an intense reactive gliosis with the presence of GFAP-positive astrocytes in the peripheral parts of the tumor.

#### 20.1.4

##### Regressive Events

The most constant and important regressive events are cystic and fatty degeneration, hemorrhage, and hyalinization.

The formation of cysts is thought to be due to the transudation of plasma from blood vessels, with a more or less constant supply of intracystic fluid [628], explaining why aspiration is usually unsuccessful. The wall of the cyst is formed by fibrous

glia and may contain Rosenthal's fibers, and also hemoglobin degradation products if hemorrhage has occurred.

Syringomyelia may develop in association with hemangioblastomas of the spinal cord [834], through a process similar to that leading to cyst formation. Others believe it is a primary feature of VHL disease [1398].

Hemorrhage is constantly present, as a discrete erythrocyte seepage into the tumor parenchyma and/or massive and extensive bleeding. Erythrocytes are found free within the tissue between the capillaries and the vascular lacunae, and also between the stromal elements where, by confluence, they may give rise to pools with no limiting endothelium. Hyalinization processes are common.

### 20.1.5

#### Electron Microscopy Study

Three cell types are recognized: endothelial cells, pericytes and stromal cells [430, 465, 1619, 3271, 483, 1346, 1348, 1349, 1350, 3169, 1578].

Stromal cells, besides vacuoles, vesicles, and lipid granules [1350], show features reminiscent of endothelial cells, such as microfilaments, serrate junctions, basement membranes, and Weibel–Palade bodies, although in lesser quantities, probably because they derive from common mesenchymal angiogenic cells [1346]. Pericytes do not contain Weibel–Palade bodies and derive from nonangiogenic mesenchymal cells. Factor VIII/RAG demonstration in stromal cells is controversial, with positive [1563] and negative observations [2201]. It is possible that there is a loss of antigen or an insufficient concentration of antigen [1346]. It must be added that the occurrence of Weibel–Palade bodies in stromal cells has also been questioned [3169], and a leiomyoblastic differentiation has been found both in pericytes and in stromal cells [1578]. Pericytes are more abundant than in the capillaries of the brain, muscle, and lung. They have a contractile function and probably regulate the size of the capillary lumen [1348]. A large number of mast cells is found in this tumor in relation to the endothelial and stromal cells. They continuously degranulate in the intercellular spaces, and the heparin released may be an important factor in the proliferation of blood vessels [1346].

Endothelial cells contain large pinocytic vesicles situated close to the nucleus and surrounded by bundles of microfilaments and Weibel–Palade bodies. The large vesicles which derive from the invaginated plasma membrane have no known function [1349].

By electron microscopy immunogold analysis it has been demonstrated that endothelia abundantly express Glut-1 glucose transporter [574].

### 20.1.6

#### Metastasis, Recurrences, Prognosis

Hemangioblastomas are biologically benign tumors, even when histologically they show a tendency to infiltrate the surrounding tissue [3295]. A permanent cure can be obtained by complete surgical removal. Recurrences can arise with incomplete

surgical removal or after a simple evacuation of the cyst. In some instances, it is difficult to establish whether it is a real recurrence or a multiple neoplasm. Recurrences, however, have also been reported also after an apparently total removal [2606]. Five years after surgery, 89% of patients were in good condition in a recent series [2406]. There are no examples of tumors which have undergone malignant change, not even in the exceptional cases of subarachnoid dissemination [2293]. An angiosarcoma of hemangioblastic derivation has never been reported.

### 20.1.7

#### Associated Polycythemia

The genetic relationship of tumor angioblasts with embryonal angioblastic tissue, apart from the morphological resemblance, is underscored by the finding of polycythemia in some cases [3215], with a return to normocythemia after tumor resection, and by the presence of islands of erythropoiesis in the tumor parenchyma [2141, 1156].

A substance similar to erythropoietin, the hormone regulating erythropoiesis which is associated with polycythemia, has been found [3591, 1293, 1516] in the cysts and in the tumor. Furthermore, 120- to 500-nm secretory granules which may be erythropoietin or its precursors have been found in stromal cells [1473, 66]. Cells immunohistochemically positive for erythropoietin and renin have also been found in the tumor [291].

### 20.1.8

#### Differential Diagnosis

The similarity between the cellular type of hemangioblastoma and paraganglioma of the cauda equina has already been remarked upon. Another distinction must be made in respect of metastatic renal cell carcinoma. The main problem remains that of the distinction from angioblastic meningioma (see Chap. 18). Fundamentally, the findings are in favor of an assimilation of the variant 3 of type IV angioblastic meningioma of Cushing and Eisenhardt [629], i.e., the hemangioblastic variant, with the hemangioblastoma [1396, 1642, 2904]. It is still doubtful whether transitional forms exist between meningioma of different types and hemangioblastoma [2904].

## Tumors and Dysontogenetic Lesions

### 21.1

#### Germ Cell Tumors

Germinal cells represent one of the cell lines into which the blastoderm differentiates, the others being the somatic and the extraembryonal lines, but at the same time germ cells are capable of differentiating again toward the somatic and extraembryonal lines. After they form in the normal yolk sac, they migrate toward the gonadal folds, but if displaced, they can retain their ontogenetic potential and acquire neoplastic properties [3602].

The various germ cell tumors (GCT) correspond to embryonal stages of development. Germinomas correspond to primordial germinal cells. The extraembryonal derivatives of germ cells may differentiate into yolk sac endoderm, thereby forming endodermal sinus tumors, or into trophoblast, hence forming chorioncarcinomas. From pluripotent embryo stem cells, according to some, embryonal carcinoma originates and then immature and mature teratomas develop, which may be mono-, di-, or tridermomas [3405] (see Fig. 21.1). According to others embryonal carcinoma represents a further stage of differentiation of endodermal sinus tumors and does not have the ability to differentiate into embryonal and extraembryonal derivatives [3378]. Still other theories exist. For example, according to the embryonal cell theory, displaced foci of embryonal cells may escape the influence of the primary organizer. According to the theory of extraembryonal cells, teratomas originating from the yolk sac are not of germ cell origin. Another theory sustains that teratomas originate from an included twin fetus [1134]. The term “teratoma” can be used with two meanings. In the strict sense, it indicates tumors which contain embryonal elements of all three primitive germinal layers. In a broader sense, it indicates any cerebral benign or malignant dysontogenetic lesion.

#### 21.1.1

##### Frequency, Age, Sites, Clinical Features, Imaging

GCT originate at specific points along the midline of the body, such as the gonads, or the sacrococcygeal, retroperitoneal, mediastinal, and diencephalic regions. Rarely, nonmidline tumors [3582, 2147, 2377, 1730] involving the basal ganglia, thalamus, frontal, and paraventricular regions or septum pellucidum have been reported [2147, 3381]. It has been calculated that no more than 40 cases have been described in the basal ganglia, plus two recent ones [3381]. These tumors have common histological

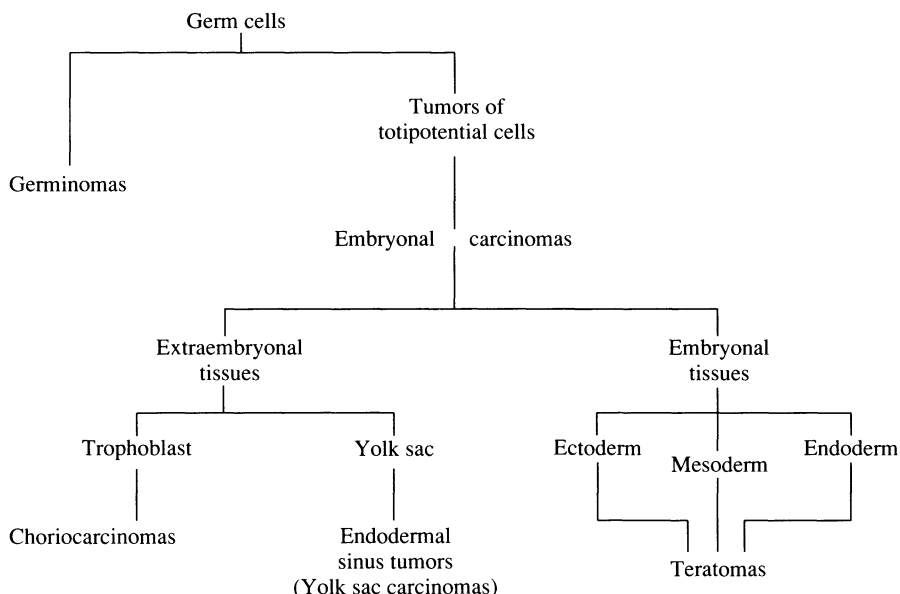


Fig. 21.1. Development of germ cell tumors (GCT)

features. They may be congenital, and in this case they are mainly benign teratomas. Teratomas of the third ventricle are, in fact, the most frequent congenital intracranial tumor [3588].

GCT arise in the region of the third ventricle, along a line which runs from the suprasellar cistern to the pineal region. Germinomas are mostly found in the suprasellar region followed by the pineal region and then by the basal ganglia/thalamus, while nongerminomatous tumors appear in the pineal region, followed by the suprasellar region, lateral ventricles, fourth ventricle and cerebellum [1537]. A case of embryonal cell carcinoma localized in the parietal lobe has been reported [1742B].

From the clinical point of view, hypopituitarism due to multiple hormone deficiencies, pituitary dwarfism, hyperprolactinemia, diabetes insipidus, hypernatremia, and precocious puberty may develop, especially if the tumor is suprasellar [1461].

On computed tomography (CT) scan, the tumor appears as a isodense or slightly hyperdense lesion with contrast enhancement. Calcification may be present. On magnetic resonance imaging (MRI), the tumor is isointense on T1- and hyperintense on T2-weighted images. It is enhanced after gadolinium.

The male to female ratio is 3.25:1 for nongerminomatous tumors and 1.88:1 for germinomas. The suprasellar region is more often involved in females, while the pineal region prevails in males [1537]. The tumors appear at the age of 10–12 years, but teratomas and choriocarcinomas are more frequent in younger children, and the incidence of germinomas peaks toward 13–15 years old [1538].

GCT represent 0.5% of all intracranial tumors [30, 1518]. A high incidence, of 4%–5% of these tumors in Japan [81, 2367, 1830] and Taiwan [3167] has been noted. In Taiwan, they represent up to 5.1% [88] or even 9% of intracranial tumors. This is va-



lid also for testicular GCT. For these tumors an increase in incidence in individuals under 30 years of age has been found since the last World War [3086].

### 21.1.2

#### **Pathogenesis**

There is no doubt that germinal cells are the source of GCT. However, it is not clear whether this is due to a defect of migration, to the formation of “embryonal remnants,” or to other causes, taking into account that almost all of these tumors originate in the suprasellar region and in the pineal region.

Embryology teaches us that maturation of the diencephalic structures coincides with migration of the germinal cells from the posterior yolk sac to the gonadal crests and that after the 60th day of gestation, there are no extragonadal cells left. A simple migration error may explain the origin of retroperitoneal, mediastinal, and sacrococcygeal GCT, but for the diencephalon, such local factors as the mechanisms of regulation of gonadotrophic activity must be invoked. Neuroendocrine events at puberty may have an activating influence, and there are many observations which indicate an inductive or a transformative role of gonadotrophin on GCT.

### 21.1.3

#### **Germinoma**

At the suprasellar and pineal sites, germinoma is the most frequent of all GCT and represents 0.1%–3.4% of all intracranial tumors [1389].

#### 21.1.3.1

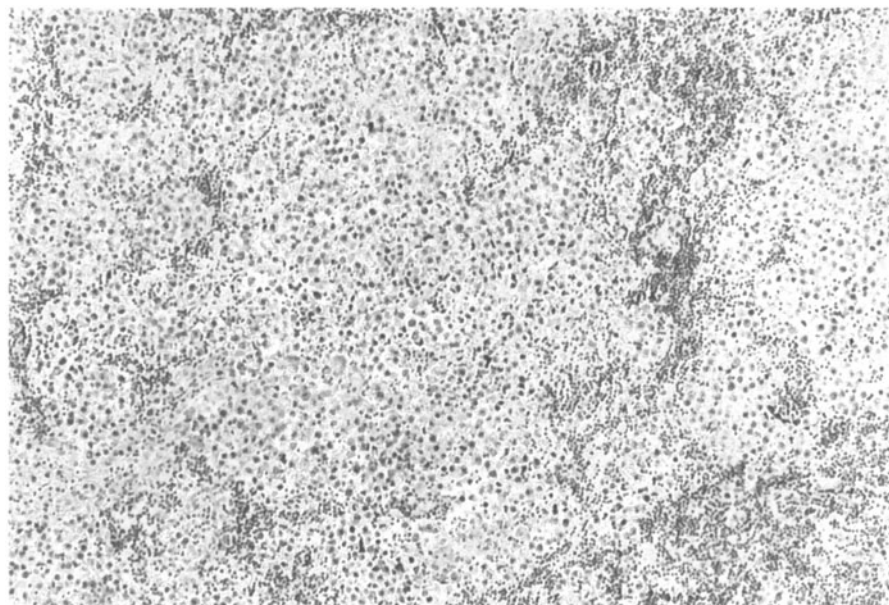
##### ***Macroscopic Appearance***

The tumor, whose cut surface is grayish-pink and friable in consistency, is at times calcified; it may appear demarcated and confined to the pineal gland but more often infiltrates surrounding areas, e.g., the roof of the third ventricle, quadrigeminal plate, aqueduct. When it develops more anteriorly, it reaches the anterior part of the third ventricle, the lamina terminalis, the chiasm, and the foramina of Monro. It may even grow into the lateral ventricles.

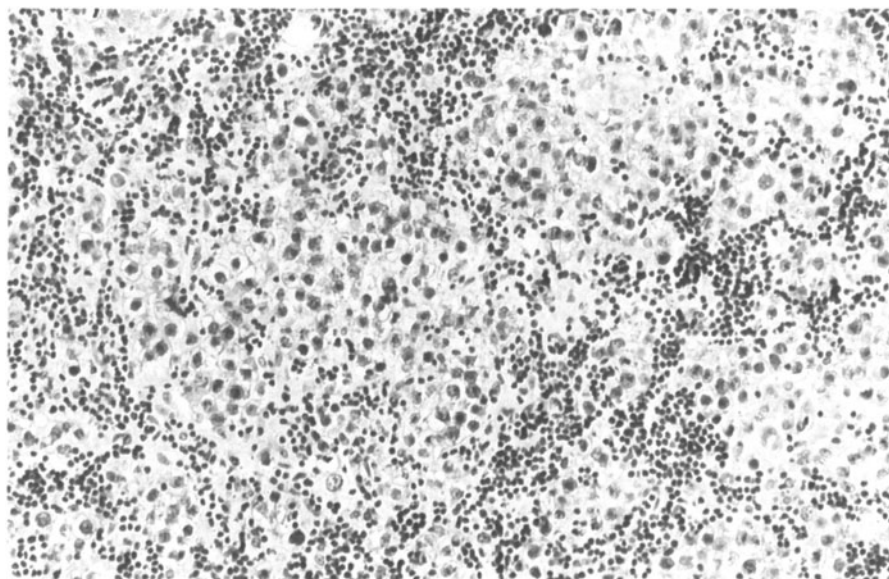
#### 21.1.3.2

##### ***Microscopic Appearance***

It recalls that of gonadal tumors and of mediastinal germinoma and features lobules delimited by fibrous septa containing lymphocytes (Fig. 21.2a). Tumor cells may also be admixed with lymphocytes. The tumor is composed of cells of two types: large and small (Fig. 21.2b). The former have eosinophilic, ill-defined cytoplasm and contain a vesicular nucleus with an evident nucleolus (Fig. 21.3). Mitoses may



a



b

**Fig. 21.2a,b.** Germinoma. **a** Lobules delimited by septa containing lymphocytes. H&E,  $\times 125$ . **b** Tumor cells admixed with lymphocytes. H&E,  $\times 300$

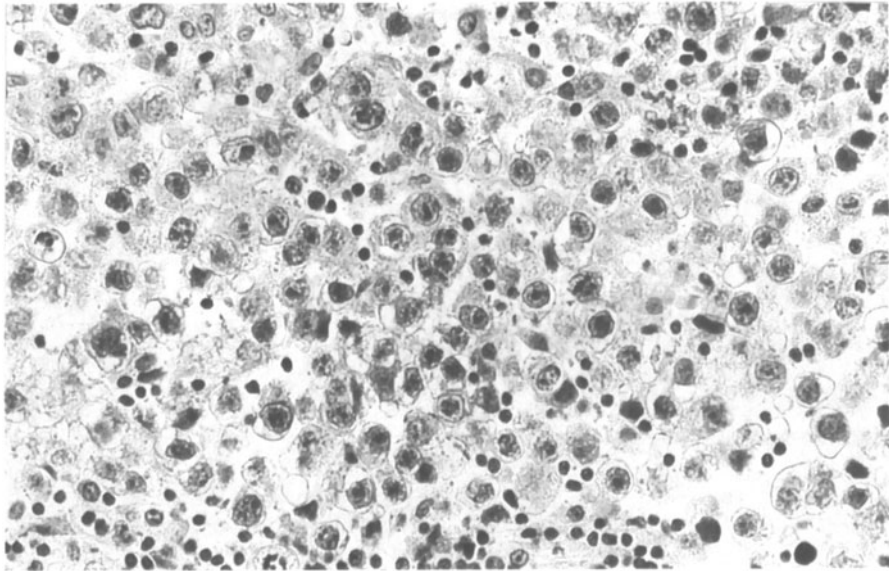


Fig. 21.3. Germinoma, typical tumor cells with vesicular nucleus and evident nucleolus. H&E,  $\times 400$

be numerous. The small cells are lymphocytes which are clustered into groups or scattered, especially in the fibrous septa. They have been found to be mostly of the T cell subset [2413]. Multinucleated, foreign body-type giant cells may occasionally be present.

Not uncommonly, the histological appearance is mixed, because of the presence of teratomatous areas or of other germinal tumor elements, e.g., embryonal carcinoma, choriocarcinoma [2167].

The cytoplasm of the large cells contains periodic acid-Schiff (PAS)-positive glycogen granules. Under the electron microscope, apart from endodermal cells and lymphocytes, mesothelial cells and large trophoblastic cells are seen. The endodermal cells show the already mentioned glycogen granules, annular lamellae, and junctional complexes [591, 1329, 2113, 3366, 1256, 1739].

#### 21.1.3.3

##### *Prognosis, Treatment*

Germinoma is sensitive to radiation and, in general, is characterized by fairly good postoperative survival rates. Its quartile is 1.4 as opposed to 0.1 for the other GCT [1538]. Undoubted advantages resulting from advances in neurosurgery in these anatomical areas [1553] have led to suggestions that surgical procedures should be attempted before other forms of therapy [3296]. Postoperative radiotherapy has given very good results [1907]: survival at 5 and 10 years has been 75% and 69% [2946] and 85.6% [2167], respectively, whilst others reported 82% survival at 5 years [803]. It should be remembered that some series in the literature are not histologically

documented. A positive response to irradiation with 20 Gy is sometimes used as a diagnostic procedure [803], but many authors do not agree.

The tumor may spread via the cerebrospinal fluid (CSF) [262] with a variable, even very high frequency [1907], so most authors advocate preventive postoperative irradiation to the entire neuraxis. According to some, this approach would not be justified when myelography and cytology results are negative [3611]. Distant metastases via the blood stream have been reported [1537].

#### 21.1.4

##### **Embryonal Carcinoma**

The embryonal carcinoma represents 31% of the tumors of the pineal region in infancy [2526], is formed of cords or lobules of anaplastic or columnar cells (Fig. 21.4), has nuclei which are vesicular and contain an evident nucleolus. Mitoses are frequent. The epithelium may take on a fibroblastic appearance, and cartilage may form within the stroma. "Embryonal bodies," likened to normal 1- to 2-week-old embryos, may be identified in the tumor [855].

#### 21.1.5

##### **Choriocarcinoma**

Choriocarcinoma is a very rare tumor: Up to 1974, 34 cases had been reported [1251]. It is rarely pure and is usually admixed with other tumor types, such as embryonal carcinoma and teratoma.

It is not possible to be certain, solely on the basis of a biopsy, whether the tumor is a pure extragenital choriocarcinoma (because nonchoriocarcinomatous portions may not have been sampled) or a cerebral metastasis from a reproductive tract tumor [263]. For this reason, the number of reports of pure cases up to 1983 was only 24 [3744]. In a series of 70 cases of germinal tumors, there was only one choriocarcinoma [262].

Histologically it is characterized by the presence of multinucleated syncytiotrophoblastic cells which surround the monomorphous cytotrophoblast and cavernous blood spaces. The tumor is found in the pineal region or, more rarely, in the suprasellar location, in the lateral ventricle [1613], or in the third ventricle [2122].

#### 21.1.6

##### **Endodermal Sinus Tumor**

This tumor is characterized by the presence of endodermal sinuses (Schiller-Duval bodies), perivascular endodermal cells, and cystic dilatations with thin walls. The tumor was described in 1968 [227], and not more than 36 cases have since been reported: 26 were located in the pineal region and eight in the suprasellar region. A case in the thalamus has also been published [2147]. The tumor is highly malignant and features a network of cuboidal epithelium forming papillae sustained by delicate

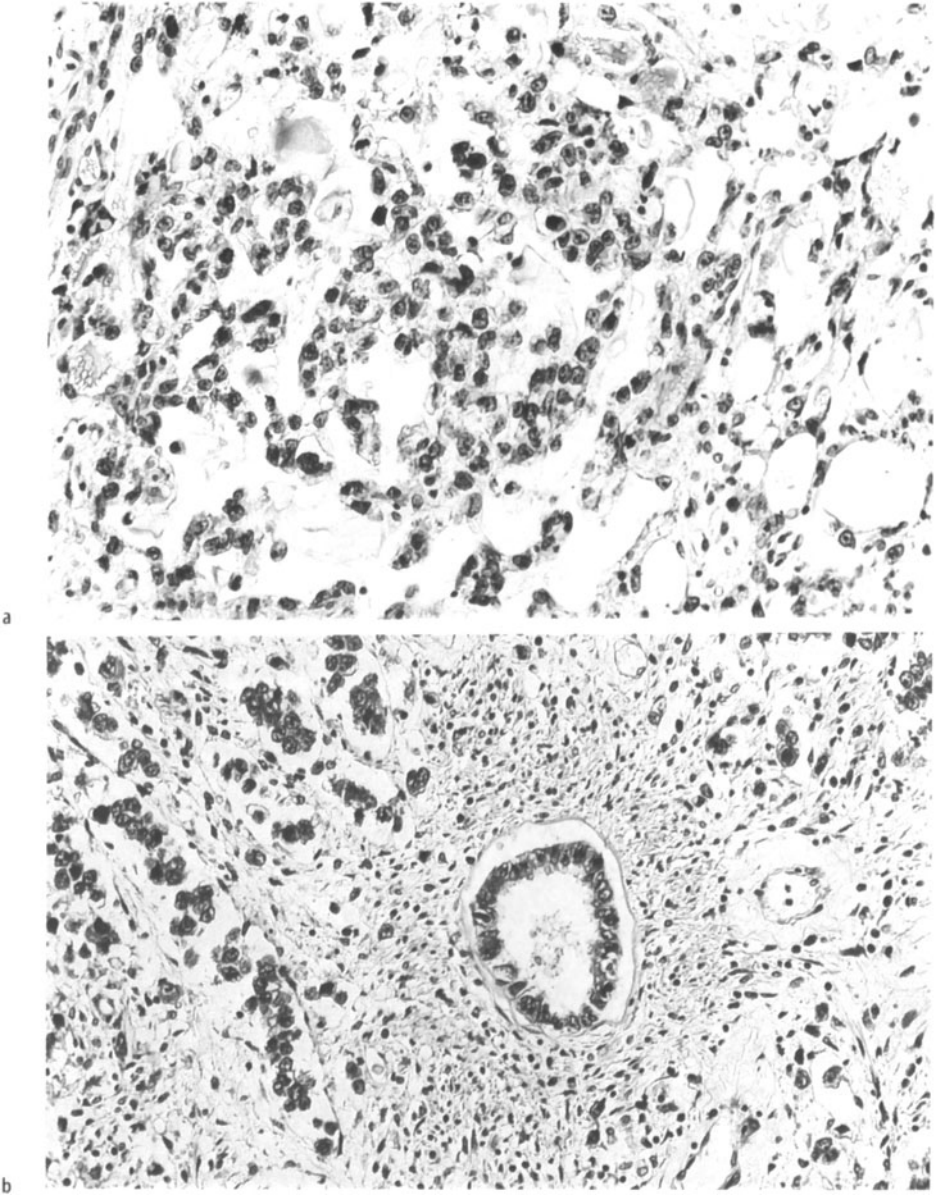


Fig. 21.4a,b. Embryonal carcinoma. **a** Cords and lobules of tumor cells. **b** Teratomatous aspects. H&E,  $\times 300$

connective tissue, containing blood vessels with thin walls. Under the electron microscope, the cuboidal or irregular cells have numerous apical microvilli, lateral serrated junctions, and a delicate basal membrane. The trophoblastic cells are similar to those found in choriocarcinoma [2147]. Beside the very rare pure forms, mixed ones with endodermal sinus tumor, germinoma, choriocarcinoma, or embryonal carcinoma have been described [1518, 2904].

### 21.1.7

#### Teratocarcinoma

The teratocarcinoma is formed by embryonal carcinoma and mature or immature teratoma. Embryonal carcinomatous features occur beside the teratomatous ones [307, 2129]. Teratocarcinoma has to be distinguished from teratomas with malignant transformation [3602]. A doubtful case of association between germinoma and astrocytoma has also been reported [2415]. Embryonal carcinoma, endodermal sinus tumor, and choriocarcinoma are highly malignant and have a poor prognosis [1537]. They tend to metastasize via the CSF.

### 21.1.8

#### Immunohistochemical and Chemical Characterization

The characterization is achieved by the immunohistochemical demonstration on tissue, and by immunochemistry on CSF and blood, of a panel of antigens such as carcinoembryonic antigen (CEA),  $\alpha$ -fetoprotein (AFP), human chorionic gonadotropin (HCG), and placental alkaline phosphatase (PLAP). AFP and HCG levels are raised in the serum and/or CSF not only in embryonal carcinomas and choriocarcinomas [1465], but also in teratomas [2372]. Germinomas are negative for AFP and CEA [3171, 262].

If HCG positivity in germinomas is demonstrated, the tumor is considered to be mixed. In contrast, germinomas are very often positive for PLAP [3171, 1465, 3614].

Germinomas have sometimes been found to be cytokeratin- and EMA-positive as well as vimentin-positive in different cells [2386]. This would demonstrate that intracranial germinomas may show early signs of epithelial or mesenchymal differentiation.

## 21.2

### Teratomas

These can be subdivided into mono-, bi-, and tridermomas depending on whether one, two, or three layers participate in the neoplastic process. Epidermoids, enterogenous cysts, cerebral lipomas, and colloid cysts of the third ventricle are examples of monodermomas [3602]. Dermoid cysts are examples of didermomas. Tridermomas are in turn subdivided into mature and immature. The former may undergo malignant transformation, while in the latter it is difficult to recognize the three layers.

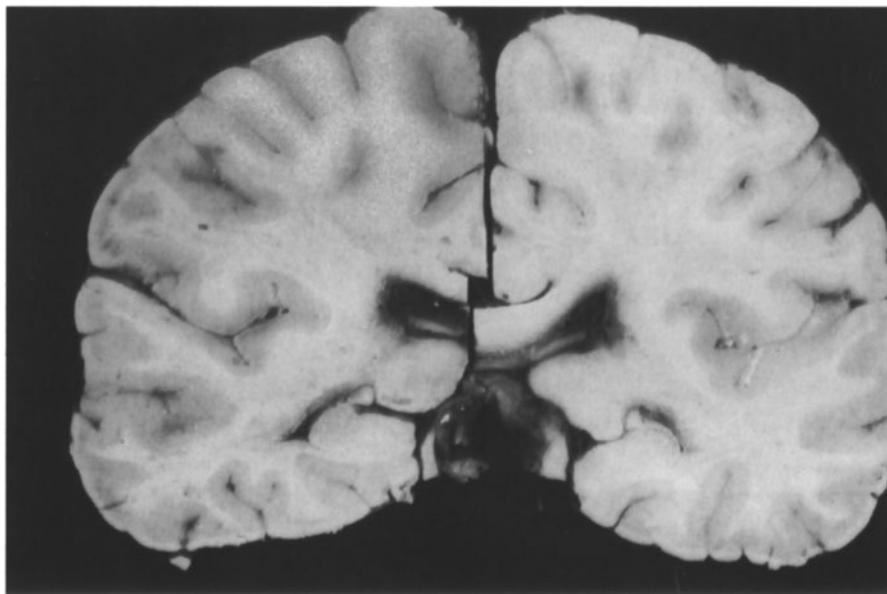


Fig. 21.5. Mature teratoma of pineal region

#### 21.2.1

##### Frequency, Age, Site

Intracranial teratomas are very rare; they comprise 0.5% of all intracranial tumors [3799] and 2% of those occurring in infancy [1463]. The frequency is higher in Japan, in agreement with that of GCT in general. In the spinal cord they are even rarer, two out of 1322 tumors [3221]. There is a predilection for men and the first two decades of life. Intracranially, they favor sites in the pineal region, the suprasellar region, the pituitary fossa, and the fourth ventricle [2994, 262, 2904]. In the spine, they appear mostly in the sacrococcygeal region.

The clinical presentation depends on the location. The imaging is highly heterogeneous, both on CT and MRI, due to the various components of the tumor. Contrast enhancement is usually irregular and heterogeneous. Malignant forms invade the surrounding structures.

#### 21.2.2

##### Macroscopic Appearance

They are mostly single, rarely double or multiple [1463]. The external appearance of typical teratomas is that of an encapsulated tumor, well demarcated from surrounding tissues (Fig. 21.5). In spinal teratomas, the tumor may be less demarcated and adherent to surrounding tissues. The surface is usually smooth and nodular, the color is reddish and often variegated, because of the numerous hemorrhages and

many brownish cysts [3799]. The consistency varies in relation to the structures present in the tumor, but in the majority of cases it is like that of cartilage. On section, the tumor is polymorphous. Cysts occur very frequently and their content is at times similar to that of dermoepidermoids, but it is often yellowish or reddish or dark-brown, because of hemorrhages. In typical teratomas, the presence of organoid formations is a macroscopic diagnostic element. In immature teratomas the limits of the tumor are not clear-cut, and it almost constantly infiltrates the surrounding tissues.

### 21.2.3

#### Microscopic Appearance

Mature teratomas present with remarkable polymorphous features which are determined both by the presence of various organoid structures and by the extension and intensity of regressive processes. In typical forms, various mature tissues of epithelial, mesodermic, and endodermic origin may be observed [2469, 1312]. In a pineal teratoma, the presence of 15 different types of tissue was demonstrated [2213]. The tumor showed a high degree of differentiation and organization, which can reach the formation of organs, such as teeth and glands. Among ectodermal structures are islands of Malpighian epithelium, cutaneous adnexae such as hair, sweat and sebaceous glands, papillary and tubular formations lined by cuboidal epithelium, and cells of neuroectodermal derivation, such as neurons and glia cells (Fig. 21.6a,b). The mesodermal structures may be represented by connective fibrous, adipose, muscle (Fig. 21.6c), cartilage, and bony tissues. In every case, cells of mesodermal and angioblastic derivation such as fibroblasts, fibrocytes, lymphoblasts, lymphocytes, plasma cells, are found. Tissues of endodermal derivation are more rarely observed, e.g., respiratory and intestinal epithelia (Fig. 21.7). Cysts are almost invariably found originating from areas of necrosis or hemorrhage. In immature teratomas, some of the adult structures of trilaminar derivation of mature teratomas may be found. However, the main differential characteristic is represented by the presence of poorly differentiated or undifferentiated cells.

Tubular structures, canaliculi of mucous epithelial cells, or columnar structures of undifferentiated cubic epithelium can be found. In some cases, the general features may be those of a choriocarcinoma. Then, their biological behavior is also similar. Areas with a seminomatous appearance are present, as well as cells in various stages of differentiation and more or less accentuated features of anaplasia.

### 21.2.4

#### Prognosis, Recurrence

In classical teratomas formed by mature, well-differentiated tissues and demarcated from surrounding tissues, total surgical removal is the rule. In this case, recurrences are not observed. Instead, in cases of partial removal, as often happens for the pineal region and for spinal cord locations, recurrences may occur, but after a long time. Mature teratomas are, therefore, tumors with benign biological and histological behavior.



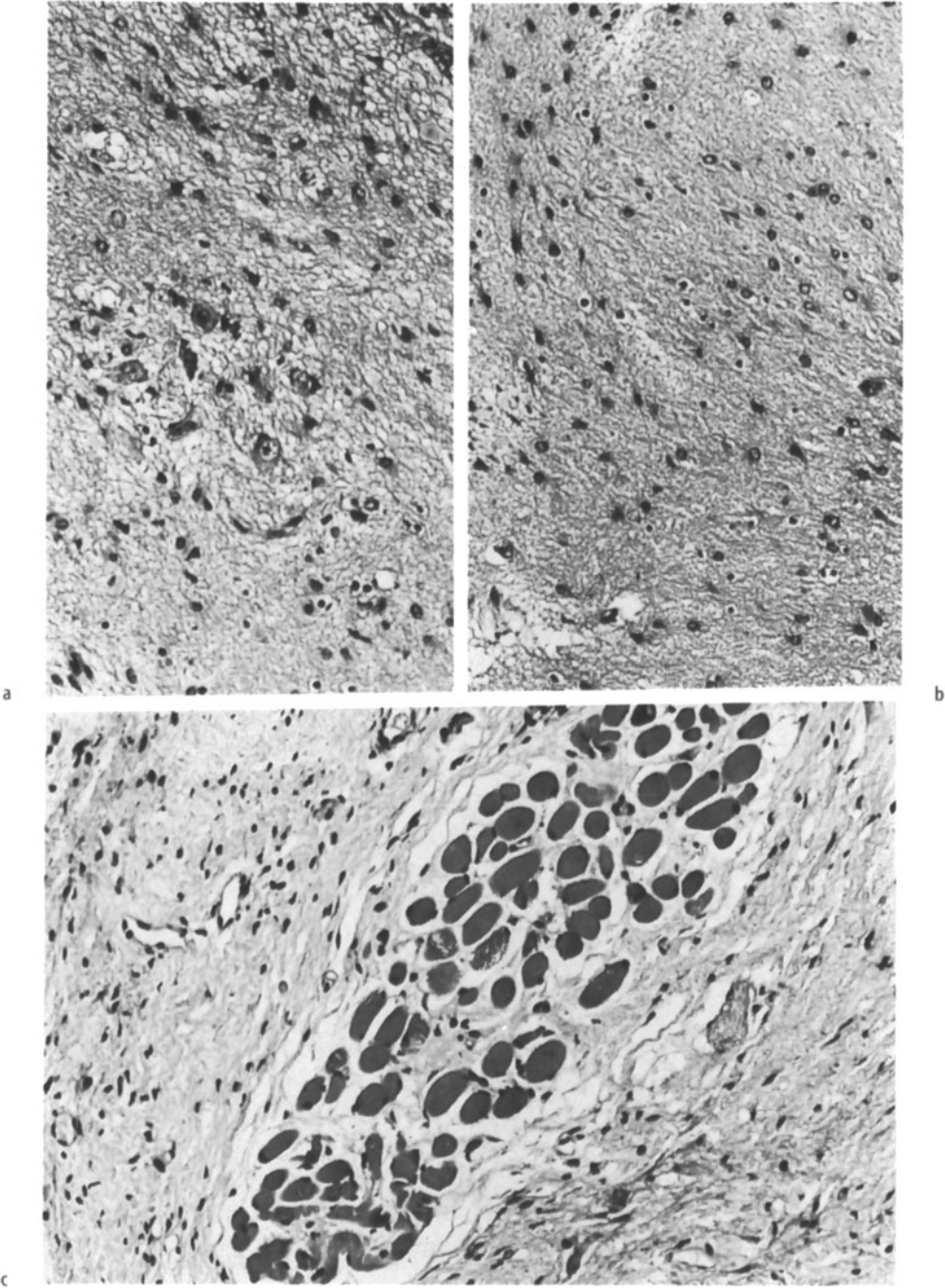
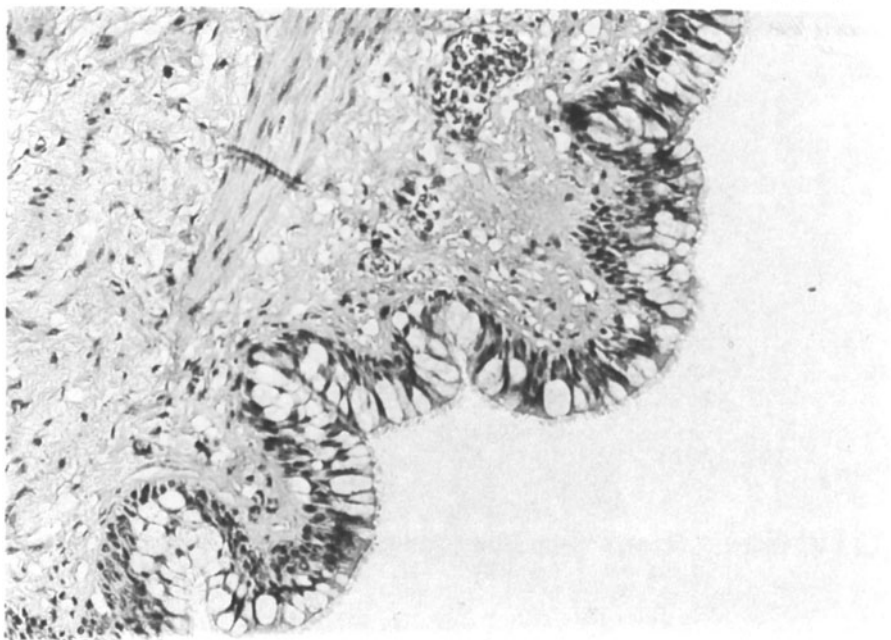


Fig. 21.6a–c. Teratoma. a Neurons. b Glial cells. c Muscle cells. H&E,  $\times 300$



a



b

Fig. 21.7a,b. Teratoma; different structures of endodermal derivation are evident. H&E, a  $\times 100$ , b  $\times 300$

Metastases have, in fact, never been reported. Tumors with multiple nodules, as occurs in other benign malformative tumors, have instead been described.

Immature teratomas may recur and even produce metastases via the CSF or outside the CNS [262]. It is very important for the prognosis to establish whether or not germinal tumor foci occur. For example, areas of embryonal carcinoma may be found [2371, 262, 3171] or, more rarely, of choriocarcinoma or germinoma evolving toward choriocarcinoma [1086]. More frequent is the finding of germinomatous areas in teratomas of the pineal region [30, 1518], suprasellar region [3204, 1518], or sellar region [2537]. Spread via the CSF is the rule in these cases, and this must not be mistaken with multicentric growths [2904].

### 21.3

#### Tumors with Muscle Cells

This section groups tumors which have in common the origin from a probable embryonal error, occurrence in infancy, affinity to immature teratomas, and presence of elements of the muscle series.

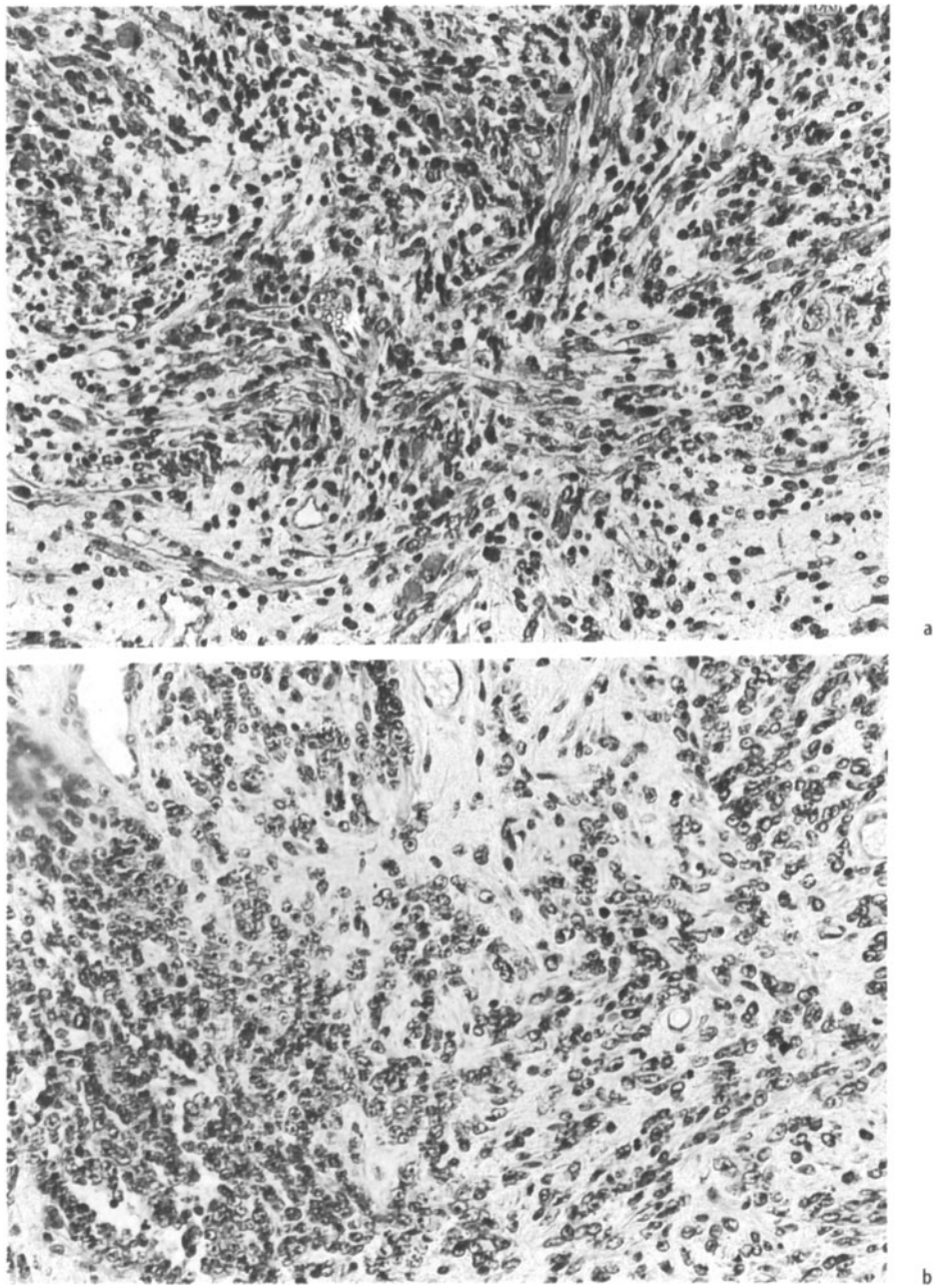
##### 21.3.1

#### Medulloblastoma

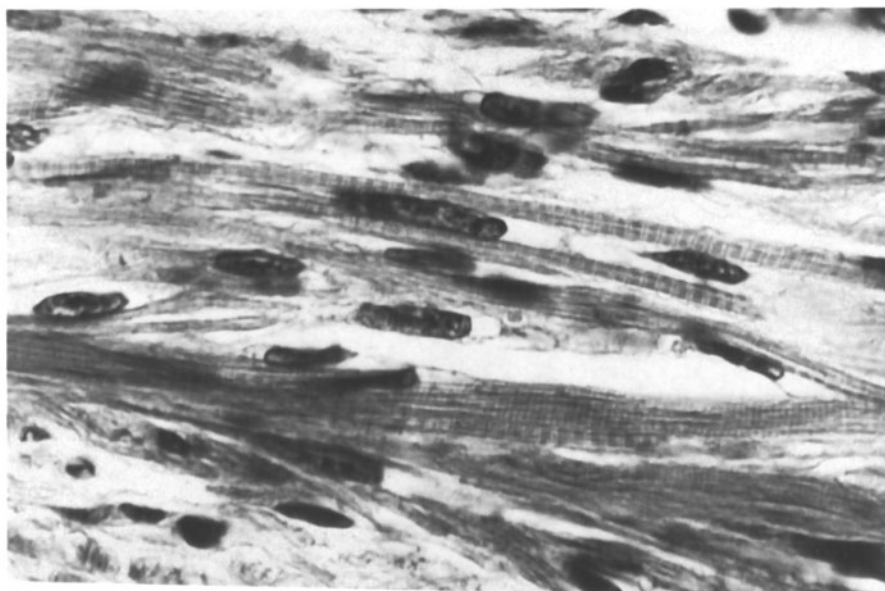
It is a rare tumor, described for the first time in a 5-year-old girl [2111]. Eighteen cases had been described up to 1985 [515]. With the recent cases [2730] there are now 25. In a personal series, there are two such cases.

The tumor has the same localization and mean age as classic medulloblastoma. Two cases have been described in adults [1010, 2730]. There is a prevalence of males, and the male to female ratio is 3.8:1. The preoperative duration is usually short, with a mean of 3.7 months; only in a few reported cases has it been longer than 6 months [286, 1191]. The microscopic aspect is similar to that of classic medulloblastoma, with the occurrence of a muscular component. This is usually represented by striated muscle fibers, distributed in bands or in perivascular areas (Fig. 21.8a). Only in two cases was the muscular component made up of smooth muscle cells [3798, 1010]. The muscular component can be easily recognized in routine histological preparations for the striated aspect (Fig. 21.9a). Confirmation may come from the immunohistochemical demonstration of desmin (Fig. 21.9b), myosin, actin, or myoglobin, or from electron microscopy study [3234, 3601]. A neuronal and glial differentiation has been demonstrated in four cases [2287, 3182, 3234, 303], whereas a glial differentiation was seen in only one case [726]. Widespread neuronal differentiation was present in two personal cases (Fig. 21.8b). A teratomatous aspect has been described in one case [515], and in some cases melanin-containing cells were found [3601, 787], bringing the tumor close to the melanotic variant of medulloblastoma.

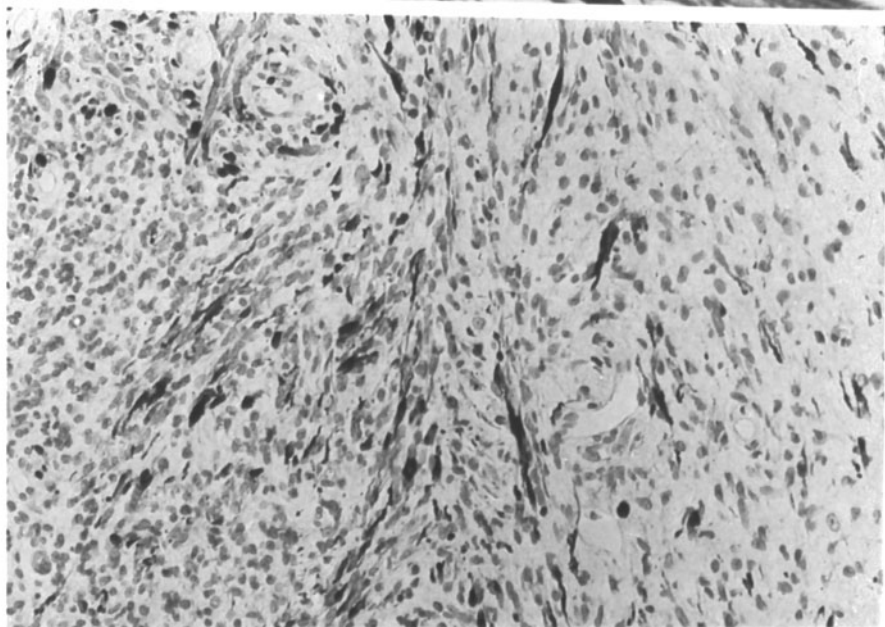
Different hypotheses have been formulated to explain the pathogenesis of this tumor. First of all, muscle cells have been thought to originate from the metaplasia of smooth muscle cells of blood vessels [2111]. Another hypothesis considers this tumor as a form of immature teratoma [515], and still another postulates that the tu-



**Fig. 21.8a,b.** Medullomyoblastoma. **a** Area with striated muscle fibers. **b** Tumor area with neuronal differentiation. H&E,  $\times 150$



a



b

Fig. 21.9a,b. Medullomyoblastoma. a Striated muscle fibers. H&E,  $\times 400$ . b Muscle fibers are positive for desmin. PAP-DAB,  $\times 200$

mor arises from primitive mesenchymal elements capable of differentiation along multiple cell lines [1191]. It is also possible that perivascular or meningeal mesenchymal elements differentiate into rhabdomyoblasts, given the frequency of their perivascular location. On the basis of the finding of muscle cells in the meninges, accompanied by glial heterotopias in children with multiple congenital anomalies [1369, 58, 2392, 1544], Russell and Rubinstein (1989) [2904] hypothesized a deviant inductive interaction.

Another hypothesis is that of origin from multipotent endothelial cells [3601], but this must be considered as very unlikely. It is also possible that primitive pluripotent ectodermal cells show a myogenic differentiation capacity [726, 3234]. One must take into account that rhabdomyoblastic differentiation has been found in a medulloblastoma cell line [123].

Survival does not differ from that of classic medulloblastoma.

### 21.3.2

#### Primitive CNS Rhabdomyosarcoma

Rhabdomyosarcoma is the most common of the soft tissue sarcomas in infancy. It arises from primitive mesenchymal cells of many tissues. In intracranial locations, rhabdomyosarcomatous features may be found in teratomas with striated muscle differentiation, in medulloblastoma or in pure rhabdomyosarcomas of which 35 cases [765] have been reported in the literature. Rhabdomyosarcoma affects young subjects, 71% of the cases being under 18 years of age, and both sexes equally. The preferred site is the posterior fossa. The tumor may primitively arise from the meninges or involve meninges and neural parenchyma at the same time. It often spreads along the craniospinal meninges.

The macroscopic appearance is varied, but rarely hemorrhagic [1899, 765].

The histological appearance is not different from that found in similar tumors in other parts of the body. Elongated rhabdomyoblasts with abundant eosinophilic cytoplasm with "racket" and "tadpole" appearances are present. Poorly differentiated areas in which cells have scanty cytoplasm and hyperchromatic nuclei may be present (Fig. 21.10), as well as loose myxoid areas. The presence of transverse striations is characteristic and diagnostic, but they are absent in about half the cases [140].

These tumors have been subdivided into embryonal, alveolar, botryoid, and pleomorphic types [1217], but this subdivision has been criticized because of the existence of a wide spectrum of variations. Under the electron microscope, rhabdomyoblasts appear at different stages of development [2692], and thick and thin myofilaments or Z band material is observed. The myofilaments may be arranged in bundles or sparsely in the cytoplasm. It is important to note that these findings may be present without transverse striations being visible under light microscopy study.

Immunohistochemically, it is possible to demonstrate myoglobin in more than 50% of tumors [346, 1570], which correlates positively with differentiation [346, 702]. The lack of demonstration of myoglobin does not, however, exclude the diagnosis of rhabdomyosarcoma. Myosin is a more sensitive indicator and, being expressed before myoglobin during development, is also present in poorly differentiated tumors [702]; however, it is less specific. Whilst vimentin is diffusely present and, therefore,

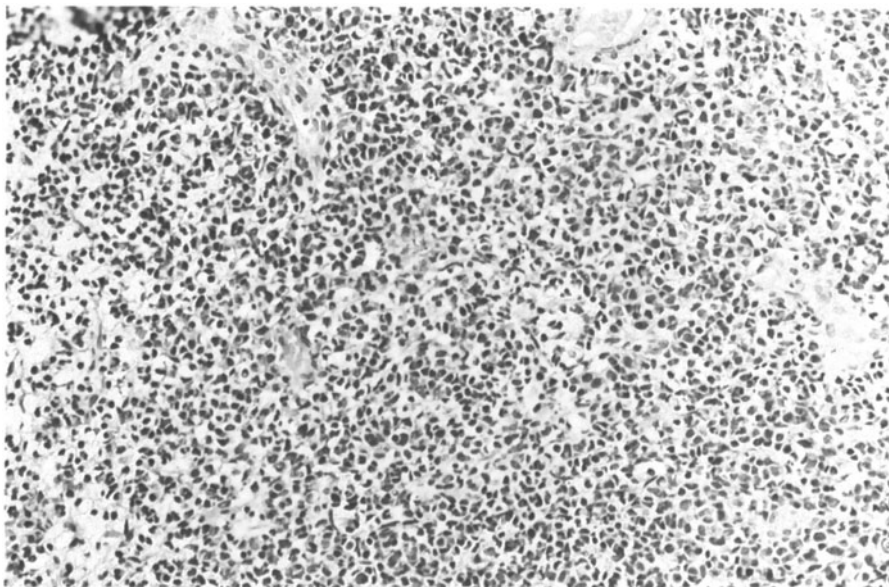


Fig. 21.10. Rhabdomyosarcoma, general aspect of a poorly differentiated area. H&E,  $\times 200$

scarcely useful for diagnosis [1322], desmin may be demonstrated in Z bands or diffusely in the cytoplasm [1570].

The tumor diagnosis is usually obtained by combining light with electron microscopy and immunohistochemistry. A still controversial question regards the origin of the cells of this tumor. In general, it is thought that they are derived from the embryonal mesenchymal pericapillary cells with the capacity to multidifferentiate, which persist after birth [276]. In the CNS, they may derive from neuroectoderm, from the so-called ectomesenchyma, or from the neural crest. It must be remembered that myoblastic differentiation with the expression of receptors for acetylcholine and myofibrils has been obtained from ethylnitrosourea (ENU)-induced glioma cell lines [1917]; these cells expressed neuron-specific enolase (NSE), in contrast to muscle cells of mesodermic derivation.

The prognosis is very closely related to the tumor site [835]; however, it has been found that for anaplastic or monomorphous tumors, the risk of recurrence is greater [2652]. Rhabdomyosarcoma has to be considered as a malignant tumor, survival being no more than 7 months from diagnosis and 10 months after at least partial surgical removal. The survival has been 9 months after radiotherapy and 8 months after combined treatment; however, there have been patients surviving 21, 42, and 67 months [765]. Radiotherapy with a dose of 50 Gy delivered to the tumor is generally advised, whereas the usefulness of chemotherapy is debatable. Local or diffuse recurrence, and not metastasis, is the main cause of death.

### 21.3.3

#### Other Tumors

Malignant mesenchymal tumors or embryonal sarcomas in which foci of rhabdomyoblastic or also chondroblastic [2870] differentiation may appear and gangliorhabdomyosarcoma [1375] may also be encompassed in this group. Gangliorhabdomyosarcomas also go under the name of ectomesenchymomas [1616] and originate from cells which migrated from the neural crest.

### 21.3.4

#### Rhabdoid Tumors

Neoplasias of infancy and childhood containing rhabdoid cells similar to those of “malignant rhabdoid tumors of the kidney” have been described as atypical teratoid/rhabdoid tumors [1902]. They have been described in different organs and sites, as well as the CNS [1902], mainly in the cerebellum but also in cerebrum, pineal region, and cerebellopontine angle.

Histologically, the tumors contain a population of rhabdoid cells and may contain fields of typical primitive neuroectodermal tumor (PNET). Areas of mesenchymal or epithelial cells may also be present. Rhabdoid cells may be small or large; in the latter, the cytoplasm is homogeneous, polygonal [508], and well defined. Nuclei show a prominent nucleolus. Rhabdoid cells are positive for EMA, vimentin and  $\alpha$ -sm-actin, and sometimes for glial fibrillary acidic protein (GFAP), neurofilaments (NF), keratin, and synaptophysin, and negative for desmin. Ultrastructurally, they are filled with intermediate filaments. Thirty-two cases have been carefully studied recently [2831]. In ten of these, chromosomal studies showed a normal karyotype in five and monosomy of chromosome 22 and a translocation of chromosome 9 and 22 with a deletion of the long arm of 22 in the other five tumors [232, 2831].

The tumor is aggressive and malignant and very rich in mitoses and commonly shows necroses. CNS dissemination is frequent. Median survival is 6.5 months, in exceptional cases longer [2831].

The origin of the tumor is still being debated. In the CNS, it has been attributed to different sources, including meningotheial precursor cells [508], embryologically similar to serosal mesothelial precursor cells surrounding the kidney and other organs. This would explain the location of the tumor in the cerebellar meninges. It is possible that rhabdoid cells represent a primitive and aggressive phenotype which may develop in a variety of tumors in different organs [2558]. It is not yet clear whether these tumors should be included in the PNET category or whether they represent a separate entity [2831].



## 21.4

### Dermo-epidermoid Cysts

#### 21.4.1

##### Nosography, Pathogenesis

The first descriptions of dermo-epidermoid cysts were made in the last century. Generally given the name “cholesteatomas” by von Müller [2346], because of the finding of cholesterol crystals in the capsule and in the cyst contents, they were also called “perlaceous tumors” [609] because of the particular macroscopic appearance.

The assimilation of epidermoid with dermoid cysts under a single heading sometimes encompassing teratomas as well has stood until today [3478], because the histological and biological differences have not been thought to be fundamental. However, such differences do exist and are sufficient to keep the two tumors separated.

The pathogenesis has variously been interpreted, but since the dysembryogenetic origin has been confirmed [2763, 314], the malformative origin has found greater consensus [1297, 3799, 801, 2904]. However, the peculiar process of embryonal divergence still remains to be clarified [2143, 1999], taking into account that, in particular cases, the pathogenetic importance, (perhaps also causal) of traumatic or inflammatory noxae has been recognized [101, 2899], especially for auricular and orbital localizations [942]. For example, the possibility of the insurgence of dermoid-epidermoid cysts in the lumbar region following lumbar puncture (especially without probe), resulting from transport and implantation of cutaneous structures within the deep tissues, has been suggested [507]. A documented case in which myelography was performed, before and after the cyst arose, has been reported [319], and this pathogenetic modality has been proven experimentally [3512] with the induction of epidermoid and dermoid cysts by direct implantation of skin in the neuraxis of an albino rat.

Like other dysembryogenetic manifestations, epidermoid and dermoid cysts are frequently associated with dysraphic conditions [2143, 1297, 2899]. In particular, spinal lesions may be uncovered by the presence of a “dermal sinus” or of spina bifida [3478] and the intracranial ones, especially those located in the posterior fossa, by related malformations [618]. The teratogenetic period has been found to be around the third to fifth week of intrauterine (i.u.) life [2624], i.e., at the time when the neural tube closes and primary cerebral vesicles form [1297, 174, 2094]. For all the craniospinal localizations, including the intraparenchymal cysts or those located in the choroid plexuses [2974, 1297], a common origin from the leptomeninges is recognized [2974, 1297]. The case in which a thoracic epidermoid cyst was associated with a meningocele is therefore of particular importance [1689].

#### 21.4.2

##### Frequency, Age, Site and Clinical Features

Dermo-epidermoid cysts are rare and represent 0.6%–2% of all tumors [1463, 1297, 2470, 174, 801, 2094, 1318, 3487, 3803, 200].

In the personal series they represent 0.54% of all tumors. Considering that the 53 cases in the collection are all intracranial, the incidence in relation to this location rises to 1.9%. Dermoids are definitely less frequent than epidermoids (1:4) [3746].

The location varies, especially for intracranial cysts [2073, 2837], which are found both in proximity to the midline and in a lateral position. The cerebello-pontine angle is thought to be the most frequent site, the rarest one being the epiphyseal region [3226]. In a large series [2073], the frequency in decreasing order was the following: cerebellopontine angle, chiasmatic region, Sylvian fissure, lateral ventricles, longitudinal fissure, diploe, parapontino-pituitary region, cerebellum, and multiple tumors at various locations. In particular, the basal parts of the posterior cranial fossa seem to be the preferred sites for epidermoids and the cerebello-medullary cistern and the cerebellum, for dermoids [1297].

For spinal tumors, a marked preference for the lumbosacral region was recognized, as with many other malformative processes.

The shape and size of the cysts influence their precise location. A more or less long peduncle may anchor the cysts to meninges or blood vessels. They grow by compressing adjacent parts of lesser resistance. Rarely, they develop on the outside of the cranium [3655].

Infants are more affected in some series [1463, 1999], consistent with the malformative origin of the cysts. However, the maximum incidence is found in the third and fourth decades of life for the intracranial and the second and third for the spinal cysts. The inconsistency may be due to the long duration of the cysts, which grow slowly, and patients survive even for decades [335, 198]; however, they are subject to growth spurts particularly in adult life. There are very young patients, for example, aged 6 months [1463], and very old ones, such as that of Henschen [1297], who was 78 years old. It can reasonably be admitted that particular local factors play a prevalent role for the biological factors.

The age at diagnosis, in personal cases, varied between 3 and 57 years with an average of 24 years, as in other series [2025, 1297]. There is a slight male predominance.

Clinical presentation is different according to the location. The common feature is that they are congenital lesions which grow slowly and become clinically evident late. Scalp cysts are mobile swellings within the dermis; diploic lesions are usually fronto-parietal, but may affect the orbital wall. Intracranial lesions are characterized by typical local symptoms of the different areas involved, and the spinal lesions are more frequently located at the conus level.

### 21.4.3

#### Macroscopic Appearance and Imaging

The tumor appears roundish and knobbly, encapsulated and well delimited, with a smooth surface. Sometimes the capsule is so thin and transparent as to allow the intracystic material to be seen. The color is usually whitish, and the consistency variable, mostly hard-elastic. On the cut surface, one or more cysts can be seen with a wall of variable thickness. In dermoid cysts (Fig. 21.11), the inner surface shows papillae, and hairs, singly or in tufts (Fig. 21.12), are visible together with material



Fig. 21.11. Midline dermoid cyst



Fig. 21.12. Hairs in a dermoid cyst

formed by amorphous greasy yellow masses of gland origin and by whitish, lamellar, friable debris produced by epithelial desquamation. In epidermoids (Fig. 21.13), the wall is thinner and the content is almost always whitish, lamelliform, and squamous. In rare cases, the content may be liquid. Calcareous concretions can be found in the cyst wall.

CT scan with bone windows demonstrates the localization to the bone with osteolysis. The lesions show low attenuation, with a tendency to calcify for dermoid cysts. On MRI, there is usually hypointensity on T1- and hyperintensity on T2-weighted images.



Fig. 21.13. Midline epidermoid cyst

#### 21.4.4

##### Microscopic Appearance

In epidermoid cysts one finds, from outside inwards, a reaction zone, an epithelial lamina, and the cyst content. The reaction zone may be glial, gliomesodermic or simply mesodermic in relation to the site. In the last, hemorrhages are frequent. Lymphocytic and plasma-cell infiltrates, both around blood vessels and free in the tissue, are constantly present; less frequently, there are polymorphonuclear neutrophil or abundant eosinophilic infiltrates. Fibroblasts, macrophages, and calcifications are present as well.

The epidermal layer is formed by a linear epithelial lamina with one to three layers of cells (Fig. 21.14); rarely, in oblique cuts, it appears as eight to ten layers. When compared with normal epidermis, the stratum lucidum and corneum are frequently missing. The granular layer instead is almost always variable but present [2837]. The malpighian layer is constantly present and is often represented by a single row of cells. The cytoplasm is frequently scanty and vacuolated. The friable and whitish material forming the content of epidermoid cysts contains large quantities of cholesterol and fat.

In the dermoid cyst, a dermal tissue occurs between the reaction zone and the epithelial lamina. Numerous sebaceous glands, of great diagnostic importance (Fig. 21.15), are usually found. The epithelium is multistratified and interlocked with the crests of papillae in the subepidermal region, which is formed by dense connective tissue. The various epithelial layers are well represented, particularly the mal-

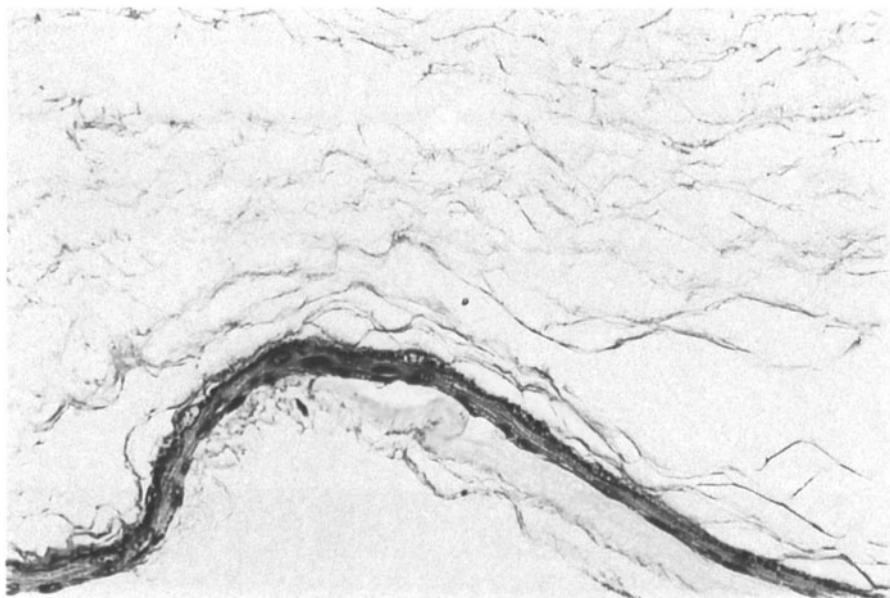


Fig. 21.14. Epidermoid cyst, epithelial lamina and desquamation product. H&E,  $\times 200$



Fig. 21.15. Dermoid cyst, epithelium and glands. H&E,  $\times 200$

pighian layer, which is very wide. The granule cell layer may be interrupted in places, and is formed by elongated cells parallel to the surface of the cyst, whose cytoplasm is often rich in basophilic granules. The epithelium, generally, does not show substantial differences from that of normal skin.

#### 21.4.5

##### Prognosis, Sequelae

The surgical removal of extraparenchymal dermoepidermoid cysts is usually technically simple. Instead, in intraparenchymal cases, especially spinal, it is difficult or impossible to carry out a complete excision. When the capsule has been completely removed, recurrences are not observed, while in the partially ablated cases, recurrences do occur but usually long after the original operation. With microsurgical techniques the long-term prognosis is good [3746, 2046].

Metastases have never been observed. The carcinomatous transformation of an epidermoid and the sarcomatous or carcinomatous ones of a dermoid are possible though exceptional events [1297, 3799, 3478, 1103].

Aseptic inflammatory reactions of meningoencephalitic type to cholesterol are possible. These may arise both spontaneously, following rupture of the capsule because of necrosis, or following operation [173].

## 21.5

### Craniopharyngioma and Epithelial Cysts

#### 21.5.1

##### Embryogenetic Aspects

Craniopharyngioma may be considered among the tumors which have caused the most discussion in neuropathology, in relation to their embryologic origin.

The tumor which is today given the name “craniopharyngioma” had already been described in 1857 by Zenker [3777], in his presentation of an autopsy case of a cystic suprasellar lesion containing cholesterol crystals and squamous epithelium. The term “craniopharyngioma” was coined in 1932 by Cushing [626], who referred to the embryologic hypothesis formulated in 1904 by Erdheim on the origin of the tumors from remnants of the craniopharyngeal duct. In the formulation of his hypothesis, Erdheim started from some observations of neuroembryology on the development of various structures of the hypophyseal region carried out years previously by Rathke and Luschka.

In 1838, Rathke described an irregular, globular invagination at the base of the skull, in the roof of the primitive stomodeum. From this structure, since then eponymously defined as “Rathke’s pouch,” the anterior portion of the hypophysis or adenohypophysis originates. Between the third and fourth week of gestation, the roof of the primitive stomodeum, which is lined by ciliated simple columnar epithelium, invaginates dorsally in the region immediately anterior to the oropharyngeal membrane, giving rise to Rathke’s pouch. The pouch later becomes elongated and forms

the orohypophyseal (or craniopharyngeal) duct, which undergoes progressive obliteration in the subsequent weeks. Towards the seventh week the duct is almost completely obliterated, remaining patent only in its cranial part, which is defined "hypophyseal pouch." At the same time, the infundibulum, which is lined by neuroepithelium, becomes elongated and protrudes posteriorly and inferiorly from the floor of the third ventricle, making contact with the hypophyseal pouch. In the meantime, the mesenchyme separates the base of the skull from the oropharynx, giving origin to the sphenoid bone and to the sella turcica.

Inside the hypophyseal pouch, the epithelium undergoes numerous infoldings until the pouch is occluded. As a consequence of epithelial proliferation, the pouch shows an anterior and superior rotational movement. The anterior and posterior walls of the folded pouch give origin to the anterior and intermediate lobes of the adenohypophysis. A small portion of the anterior wall further folds upwards, surrounds the infundibulum, and gives rise to the "pars tuberalis".

As has been said, the craniopharyngeal duct becomes obliterated, and as a rule it disappears. However, in 1860, Luschka described the presence of epithelial cells of squamous type in the infundibular region, which Erdheim interpreted as due to a phenomenon of aberrant persistence of embryonal residua of the craniopharyngeal duct. According to Erdheim, the upward rotational movement of the hypophyseal pouch, associated with the persistence of residua of the craniopharyngeal duct, is the cause of their dislocation in a suprasellar position along the anterior and lateral surface of the infundibulum. These nests of squamous cells could sometimes develop a proliferative capacity, thus giving rise to craniopharyngiomas.

Frazier and Alpers [952] and Cushing [626] referred to this pathogenetic hypothesis. The latter author was the first to use the term "craniopharyngioma," thinking that the cell remnants from which the tumor originated arose from an "imperfect closure of the hypophyseal or craniopharyngeal duct." Other authors agreed with this interpretation [3801, 1059, 1060, 2350, 2627, 1057, 2217], but the dysembryogenetic-malformative hypothesis on the origin of the tumor was not accepted by everyone [2050, 2871, 2902]. The strongest criticism was that presumably squamous epithelial cells were not primitively present, but derived by metaplasia from adenohypophyseal cells. It has in fact been demonstrated that the implant of "pellets" of tar compounds in the adenohypophysis of the rat may cause squamous metaplasia and also the development of epitheliomas [486].

The possibility was hypothesized of the squamous metaplasia of hypophyseal cells, in particular of the pars tuberalis, as the basis of the origin of craniopharyngiomas, by demonstrating the presence of squamous cells in 333 of 1364 normal pituitaries [2050]. According to these authors, squamous metaplasia has a progressively greater incidence in every later decade of life. However, subsequent observations have demonstrated nests of squamous cells even in the adenohypophysis of neonates [1117]; in this case, it would be more opportune to speak of a congenital origin of such nests rather than of metaplasia. An attempt to unify both theories, dysembryogenetic and metaplastic, has recently been made [1569, 3438]. Two histologically distinct types of tumor are noted: an infantile one, resembling the epithelium of the tooth and of the oral mucosa, of dysembryogenetic origin, and an adult one lacking some of the histological characters of the former and with a tendency to form palisades and calcifications of probable metaplastic origin from adenohypophyseal cells.

The resemblance to the tooth is at the basis of a third hypothesis sustained by different authors [179, 1575, 3114, 52], i.e., the origin of the tumor from an aberrant migration of tissue from the enamel. In this direction, the term “adamantinoma” or “ameloblastoma” with which the craniopharyngioma was often defined [598, 952, 1480] would be more appropriate. Such a relationship is demonstrated by the recognition, though rare, of tooth elements or even of well-formed true teeth among the neoplastic tissue [179, 2630, 1575, 52]. However, other authors [2902] believe that craniopharyngioma cannot be considered identical to the adamantinoma of the jaw, because of numerous histological differences.

The dysembryogenetic theory of Erdheim, reenacted by Cushing, maintained that nests of purely intrasellar squamous cells should give rise to tumors with the same frequency found in a suprasellar location, and it has been criticized [2904]. Pure intrasellar craniopharyngiomas have never been reported. Similarly, reports of craniopharyngioma of the pharyngeal hypophysis are lacking, even though nests of squamous cells have been described at this site. Craniopharyngioma could be likened to epidermoid cysts which can be found in proximity to the midline along the neural axis and of likely malformative origin, i.e., to heterotopia of ectodermal elements which occurred during the closure of the neural groove. Also, the distinction between craniopharyngioma and suprasellar epidermoid cysts would be histologically unfounded [2627].

The embryological considerations on the origin of the hypophyseal structures above mentioned are also relevant to explain other cystic malformations found relatively frequently and usually in the hypophyseal region [952, 176, 3132, 219, 1059, 2902, 2792]. They are small, purely or mainly intrasellar cysts covered by cuboidal epithelium and discovered at autopsy. In rare cases they can, however, be quite large and cause an endocrine symptomatology or that of the empty sella syndrome [1087, 3754, 1728, 139, 3540, 2374, 3300, 2863].

These structures are defined as “cysts of Rathke’s fissure” because they are supposed to originate from Rathke’s pouch, of which they represent the postnatal residue [3801, 2902, 1372, 1373, 3754, 2166]. They have a possible common embryological origin with craniopharyngiomas with which they, in fact, share histological features. In this sense, they would corroborate the dysembryogenetic hypothesis of Erdheim on the origin of craniopharyngioma.

## 21.5.2

### Incidence

Craniopharyngiomas represent 1.2% of all intracranial tumors [3803]. They can affect both sexes and all ages in equal measure, showing, however, a predilection for the first two decades of life; more than half the cases, in fact, occur in children and adolescents.

Considering patients under 20 years of age, they represent 8%–13% of all cerebral tumors [146]. A peak in patients between 6 and 10 years of age has been reported. Craniopharyngiomas have also been described in neonates [1480, 2902], and the rarity of such observation is supposed to be due to the slow growth of the tumor. A bimodal age incidence with a second peak between 50 and 70 years has been reported [2902, 1569, 2627, 441, 2217]. When all suprasellar tumors are considered, the inci-



dence of craniopharyngioma in children and adults increases to 54% and 20%, respectively [409].

The association with other oncotypes is an extremely rare event. A case of a suprasellar craniopharyngioma associated with a cystic temporal astrocytoma was reported [443]. The association in different individuals of the same family of gliomas and craniopharyngiomas has been reported as well in two families [3590]. The contemporaneous presence of arteriovenous cerebral malformations at different sites has also been noted [2316, 3253].

### 21.5.3

#### Site

The site is typically suprasellar. In a large series encompassing only adults, this site appears in 94% of cases [2627]. The contemporaneous intrasellar development is present in 18% of cases at diagnosis, but increases to 31% at autopsy [2627]. The pure intrasellar location is discussed [2902, 2217]. Russell and Rubinstein [2902] describe rare cases of dumbbell-shaped tumors developing through the diaphragm of the sella turcica. The intrasellar development of the tumor leads in general to compression or even to the destruction of the hypophysis.

Rarely has the presence of an ectopic hypophyseal gland been described in association with a craniopharyngioma [694]: In this event, the ectopic position of the gland is not supposed to be congenital, but secondary to the growth of the tumor with consequent dislocation of the hypophysis.

From the primitive suprasellar site, the tumor may subsequently expand and involve adjacent structures such as the optic chiasm anteriorly in 35% of cases [2627], and the posterior, anterior, and middle cranial fossae in decreasing order of frequency [2316]. It has been demonstrated [2217] that the variation of the length of the optic nerves and hence the position of the chiasm may condition the direction of development of the tumor. Prechiasmatic craniopharyngiomas would tend to expand toward the anterior cranial fossa. On the contrary, when the chiasm is situated very anteriorly, the tumor develops mainly toward the interpuncular fossa below, and toward the floor of third ventricle above.

Vertically, the extension of the tumor has been classified in five grades: in the fifth grade it extends from the cistern to the septum pellucidum or the third ventricle [2938].

Preferential sites in relation to age have been described [1569]. In children, craniopharyngioma grow predominantly suprasellar, while in adults it grows more commonly behind the sella, above the dorsum sellae, and in the interpuncular cistern. This site difference is related to the developmental lines of the cerebral structures along which, as the cerebral hemispheres enlarge, the third ventricle and the brain stem occupy a more dorsal and caudal position in relation to the sphenoidal plane. In an exclusively intrachiasmatic case, the malformative nature of the lesion in relation to an ectopic migration of squamous cells from the hypophyseal peduncle inside the chiasm has been hypothesized [776].

The local invasiveness of craniopharyngioma appears to be more frequent than usually thought. The percentage of tumors involving the anterior, middle, and pos-

terior fossae increases to 5%, 2%, and 4%, respectively, when autopsy cases are considered [2627].

Growth through the tentorium as far as occupying the cerebello-pontine angle has exceptionally been described [2316, 50]. Another case with abnormal extension to the nasopharynx, oropharynx, and orbits was also reported [2077].

Craniopharyngioma does not, as a rule, infiltrate the neural parenchyma; it shows extraneural growth only, even though it can have strong adhesions to the nervous tissue due to an intense reactive gliosis and to tumor digitations into the neural parenchyma. Direct invasion of the cerebral parenchyma has, however, occasionally been described, with destruction of the hypothalamus, basal ganglia, and brain stem [1480, 1178, 3583].

### 21.5.3.1

#### *Intraventricular Tumors*

The upward development of the tumor may lead to involvement of the third ventricle and cause internal hydrocephalus because of blockage of the CSF circulation. In the majority of cases, the tumor grows in the suprasellar cistern until it invaginates the floor of the third ventricle [1126], in fewer than four of 100 cases [2316]. Sometimes the tumor cyst may rupture into the ventricular system. A true communication between the tumor cyst and the ventricle has also been described [2741].

Pure intraventricular growth is very rare [739, 448, 2895, 1126, 3054]. Occasionally, it is not a primitive, intraventricular tumor, because a peduncle formed of blood vessels and stroma and even without traces of neoplastic tissue may represent the connection between the extra- and intraventricular growth [3054].

Some semantic confusion about pure intraventricular craniopharyngiomas arises from the histological similarity with epidermoid cysts of the third ventricle, which in some series are included among colloid cysts in this location [448].

As for the pathogenesis of pure intraventricular craniopharyngioma, it has been hypothesized that it develops from epidermoid cells situated in the floor of the ventricle in the region of the tuber cinereum [2895, 1126]. The pure intraventricular craniopharyngioma presents some histological peculiarities, such as an absence of calcifications and of cysts [2895, 1126], but they have not been confirmed in other reports [448, 3054].

### 21.5.4

#### *Clinical Aspects*

Apart from focal neurological signs, the most important clinical symptoms are those of intracranial hypertension. They are, in general, more pronounced in children [1770, 1366] and are attributed to the greater tendency of the tumor to grow above the sella toward the third ventricle until the foramina of Monro become obstructed.

Visual disturbances are very frequent. Apart from papilledema, visual, perimetric, and other deficits (e.g., uni- or bilateral temporal hemianopia, homonymous hemianopia, optic atrophy) are present. Other negative effects are due to endocrinopathies:

loss of libido due to a deficiency of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) and a picture of hypothyroidism due to deficiency of thyroid-stimulating hormone (TSH) [3358]. In children, precocious puberty [409], diabetes insipidus, obesity, and hypothyroidism are often observed [1366].

Typically, a child with craniopharyngioma is described as short, obese, dull, almost blind, and with a poor school record [2551].

The deficit of stature is characteristic [441]. A rare manifestation of craniopharyngiomas in adults is the amenorrhea-galactorrhea syndrome [83, 1015]. This is caused by hyperprolactinemia, whose genesis is related to a deficit of secretion of prolactin inhibiting factor, due to compression of the hypophyseal peduncle by the tumor.

Intraventricular craniopharyngiomas have a different symptomatology. Endocrinopathies are, in fact, rare, and among these may be diabetes insipidus. Similarly, visual disturbances due to involvement of optic pathways are rare or absent. Characteristic and precocious is instead the symptomatology due to obstructive hydrocephalus with headache and progressive dementia [2895, 547].

Lastly, the rupture of the cysts may cause an aseptic meningitis due to the irritating action of keratin or cholesterol [2571].

Beside clinical manifestations, laboratory results have to be briefly mentioned. The most frequent sign is represented by calcifications on a plain skull X-ray. These may be present in at least 47% of adults [2627] and up to 80% of children [1569, 441]. Much more frequent in the suprasellar region, they have also been described within the sella [1569]. In this case, the incidence is at least 4 times greater than that found with pituitary adenomas [409]. Other details which may be found on a plain X-ray of the skull are changes of the sella [2627]. In children, the enlargement of the sella is very frequent, while in adults, the erosion of the dorsum is more typical [1569].

CT scan imaging has further refined the diagnostic investigations, permitting a higher percentage of positive findings than the straight skull X-ray [3740]. The more characteristic densitometric alterations are three: calcifications, cysts, and "enhancement" after contrast medium administration [409]. Of great help is MRI.

Suprasellar calcifications, enlargement of the sella, and erosion of dorsum sellae and anterior clinoids are the main findings with plain skull X-ray films. CT scan makes it possible to distinguish solid parts from cysts, with a good enhancement of the capsule after contrast. Bone erosion and calcifications are well visualized. MRI provides additional information about the anatomic situation, and T1-weighted images provide information about the cholesterol content of the cysts. Solid parts are enhanced on T1-weighted images after injection of gadolinium. The sagittal and coronal images are indispensable for surgical procedures. Angiography may help in identifying the major vessels and their displacement. A preoperative endocrine investigation is also an indispensable tool [2087].

### 21.5.5

#### Macroscopic Appearance

Craniopharyngioma presents as two main types: solid and cystic (Fig. 21.16). The cystic type is more common, but both may coexist. In an adult series [2627], 60% of the craniopharyngiomas were purely cystic, 9% predominantly cystic, and 15%

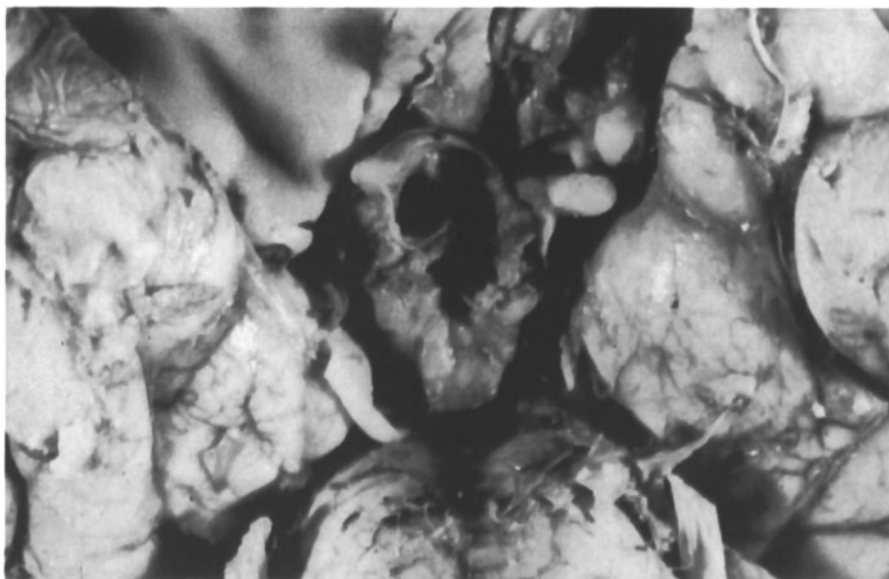


Fig. 21.16. Cystic craniopharyngioma

mixed. In a series of adult and infantile cases together, the solid type prevailed [2902]. The cysts may be of various dimensions, involve only the region of the tuber cinereum, or may expand and damage surrounding structures to reach remarkable dimensions [1728, 2741, 2376]. As previously seen, in the rare event of supra- and intrasellar development through the diaphragm of the sella, the tumor takes on a dumbbell shape [2902].

The tumor has, in general, well-defined borders (Figs.21.17, 21.18), but may present clear adhesions to surrounding nervous tissue, in which it elicits marked reactive gliosis. It is therefore debatable whether a limiting capsule is present [547].

The average dimension at the time of operation is 3.5 cm [2627]. The surface is smooth or irregularly nodular. If the tumor is predominantly of the cystic type, it can simply be formed by a thin translucent membrane, while the solid component is reduced to an intramural nodule bulging in the cyst. The solid parts have a gray-red color and show an increased consistency, caused by the presence of calcifications. On the cut surface, they are gray and granular and often contain multiple foci of calcification, bone, and deposits of degenerated fat.

The cyst content is variable: In the majority of cases, it is dense, green-brown, greasy, and very rich in cholesterol crystals. In other tumors, instead, the cysts contain a clear, amber, gelatinous, or even dense or pasty fluid.

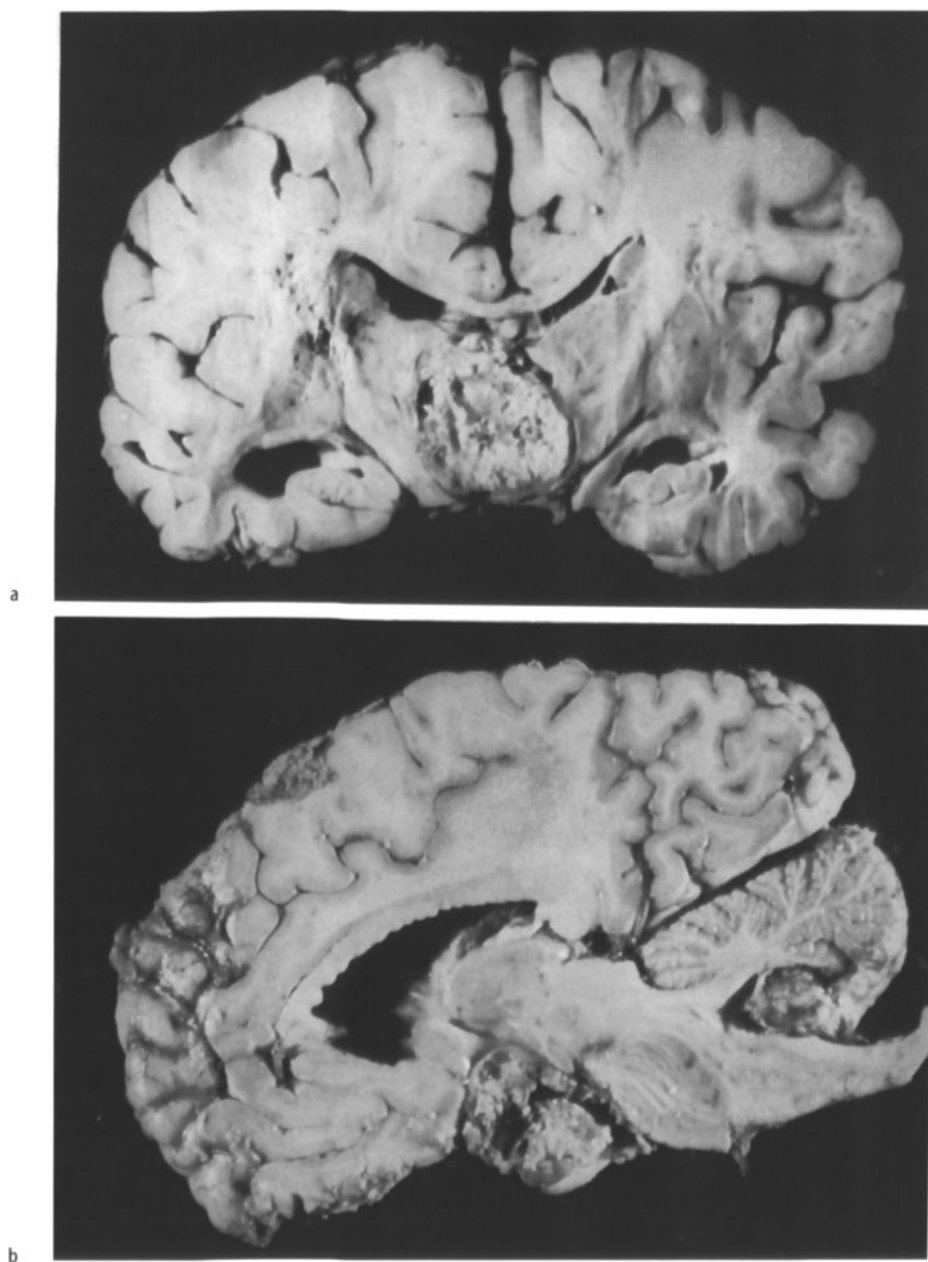


Fig. 21.17a,b. Craniopharyngioma. a Coronal section. b Sagittal section



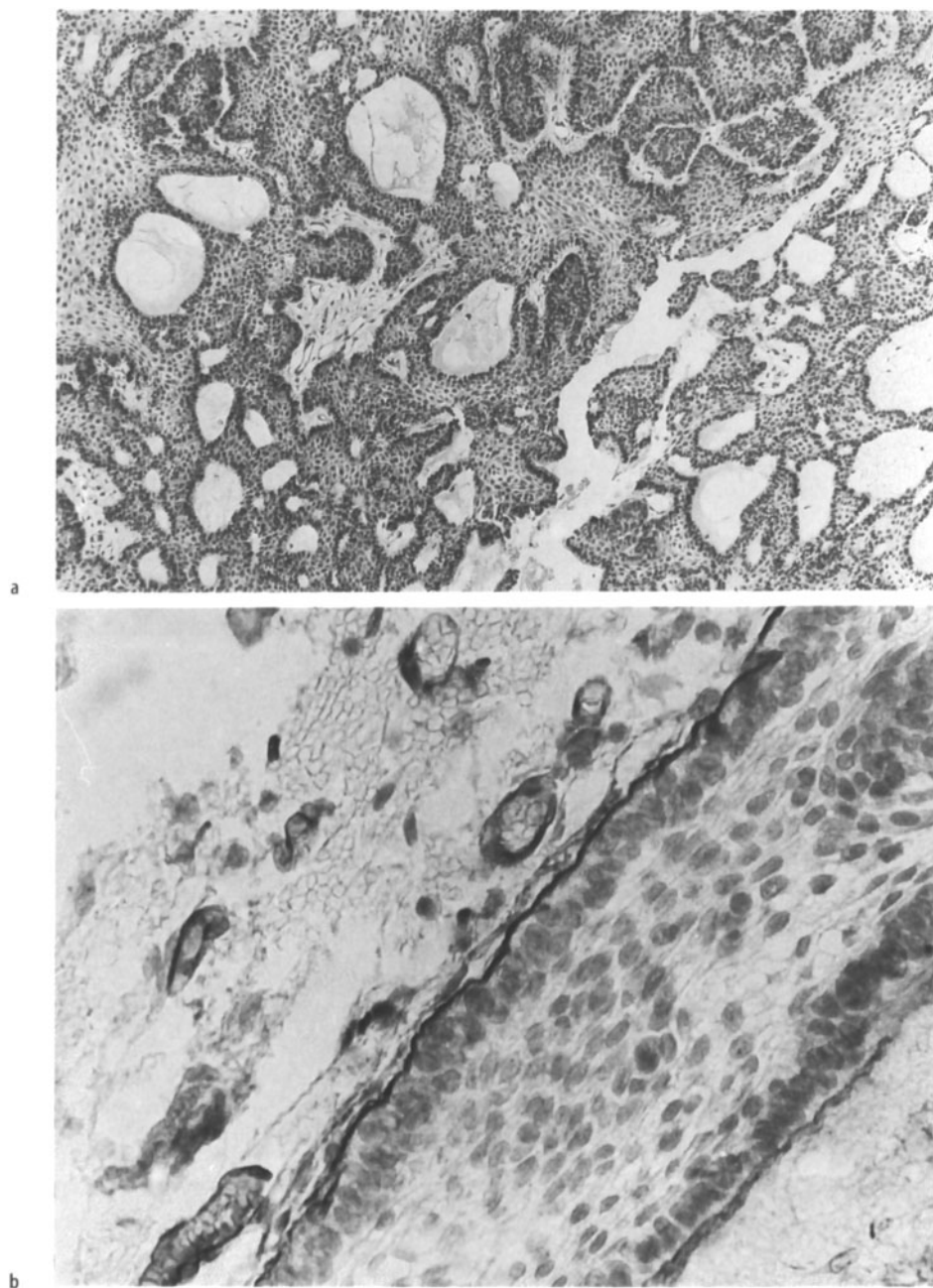
Fig. 21.18. Craniopharyngioma from the skull base

#### 21.5.6

##### Microscopic Appearance

Two components may be distinguished, cellular and cystic. Craniopharyngioma can be defined as an “epithelial microcystic tumor” [2871], formed by nests or trabeculae of variously anastomosed epithelial cells separated by a vascular connective tissue stroma (Fig. 21.19a). Cells within nests and in the trabeculae have a polygonal appearance, like those of the squamous epithelium, and are often multilayered. In these cases, it is sometimes possible to recognize differences between the various layers, almost as if the cells take up the arrangement found in the epidermis. A columnar, cuboidal, intermediate, and spinous cell layers are recognizable [2994].

The columnar cells have a central nucleus with longitudinal intracytoplasmic fibrils like the cells in the basal epithelia [2902]. The columnar cell layer delimits the periphery of the nests and rests on a basement membrane which, in turn, separates



**Fig. 21.19a,b.** Craniopharyngioma. **a** Epithelial nests and trabeculae with cysts and stroma. H&E,  $\times 150$ . **b** Basement membrane between epithelial nests and stroma. Laminin, PAP-DAB,  $\times 400$

the epithelial nests from cystic spaces or stromal trellises (Fig. 21.19b). The squamous epithelium often shows features of full “maturation,” giving rise to whorl structures and to foci of keratinization, sometimes with the formation of true keratin pearls (Fig. 21.20a).

Beside areas with squamous epithelium, other areas have been described, often in the same tumor, in which the columnar cells take up a ramified or stellate appearance and show numerous thin prolongations. These cells appear dissociated because of the presence of a finely fibrillar matrix and, consequently, give the tissue a trabecular appearance, maintaining reciprocal points of contact only through thin prolongations. The inner zones of these areas often undergo degenerative changes, so that the most centrally situated cells lose their fine cytoplasmic processes. The tissue then takes up a cribriform appearance because of the presence of numerous microcysts. These areas are often defined as “adamantinomatous” (Fig. 21.20b), in that the resulting tissue is reminiscent of the appearance of adamantinomas of the jaw [179, 2630, 179, 1575, 3114, 52].

Similarly, the extreme similarity of the stellate cells of these areas with the reticular stellate cells described in the pulp of the tooth during tooth formation has been stressed [598, 1059].

The origin of craniopharyngioma from the primitive stomodeum [839] could itself facilitate odontogenesis within the tumor. In fact, rare observations on craniopharyngiomas in which tooth formation was evident have been made [179, 52, 179, 1575, 3114]. In one case [52], admixed with tumor tissue, 20 teeth were present, the majority of which were well formed.

The term “adamantinomatous” is also used by some [952] to refer to areas in which columnar cells form palisades, which recounts the arrangement described for ameloblasts of the enamel. This reference is, however, improper because in craniopharyngioma the cells tend to be stratified, while the ameloblasts are arranged in a single layer [2902]. Russell and Rubinstein [2902] defined as adamantinomatous those tumor areas in which trabeculae of degenerated and dissociated columnar cells take up an appearance similar to that of the mesenchymal tissue produced by ameloblasts during enamel formation. In their opinion, therefore, the analogy is only descriptive and not embryological. However, others maintain that ameloblasts may as well be considered epithelial in nature, despite their resemblance to cells of the connective tissue, and sustain the correspondence (not only descriptive but also embryological) between ameloblasts and the stellate cells of craniopharyngioma [1059].

Adamantinomatous areas often arise within squamous areas or are surrounded by a single layer of columnar pseudostratified cells resting on a thin basal membrane. In other cases, cell nests may be formed by areas with adamantinomatous features in whose center squamous cells are found.

The mixture between the two cell types, seen on light microscopy study, gives evidence of a common origin, the stellate cells deriving from the squamous ones because of degenerative phenomena. The limits between areas with one cell type and areas with the other cell type may also be clear-cut, whereas in still others, transition zones may be found. Often the tumor may be totally squamous or adamantinomatous. Some authors [1569, 3438] believe that two different histological types of craniopharyngioma can be distinguished. One type is typical of children, but can also be observed in adults, and it is analogous to that described above. A second, rarer



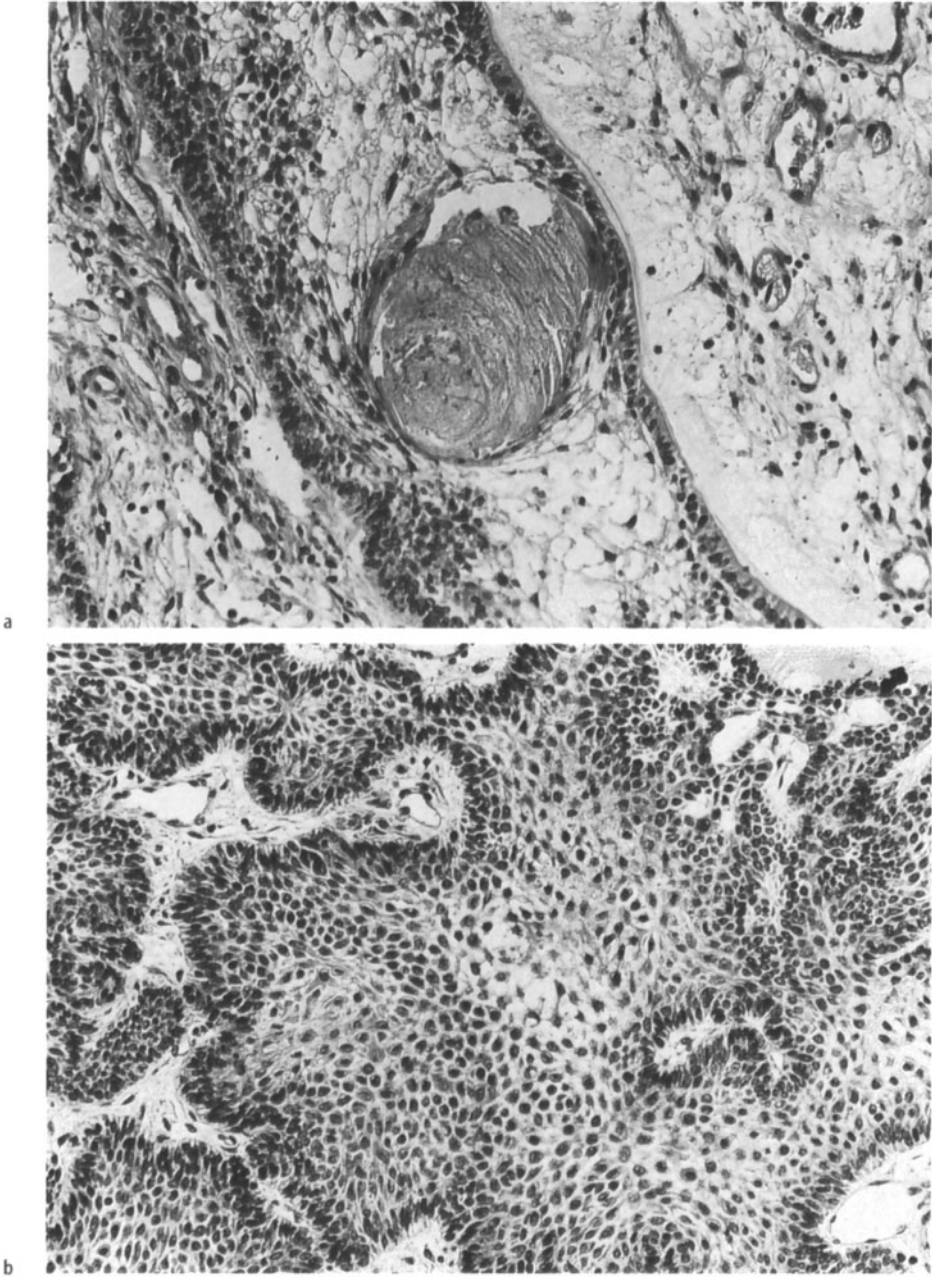


Fig. 21.20a,b. Craniopharyngioma. a Keratin pearl. b “Adamantinomatous” areas. H&E, ×400

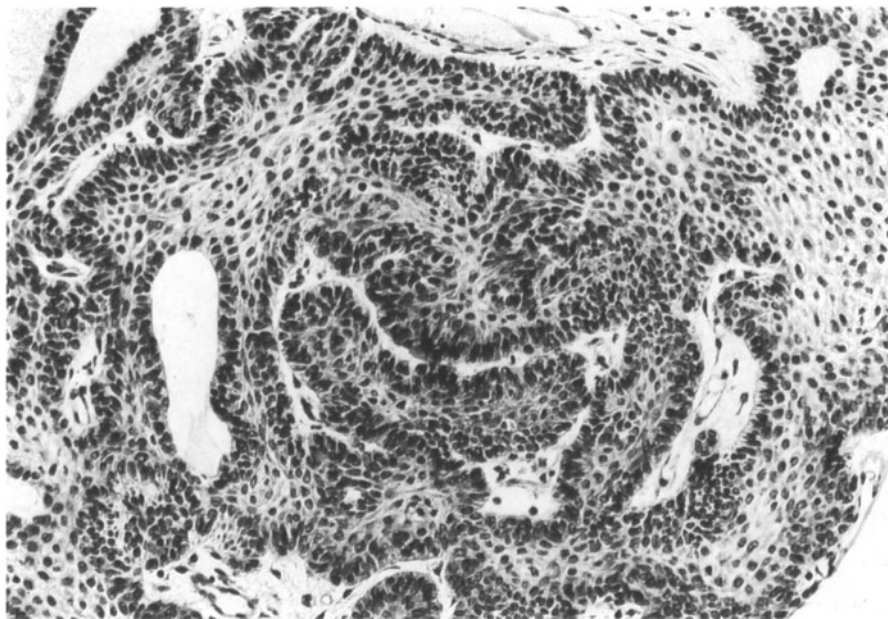


Fig. 21.21. Craniopharyngioma, papillary appearance. H&E,  $\times 400$

type occurring in adults is characterized by an epithelium which forms islands, delimits small cysts, and lies immersed in a connective tissue matrix or makes contact with nervous tissue. Neither keratinization nor calcifications are observed, and cell degeneration and the formation of large cysts are rare. This second type originates by metaplasia of suprasellar nests of squamous cells, as described by Luse and Kernohan [2050].

Craniopharyngiomas with a papillary appearance (Fig. 21.21) have recently been described in adults [1067]. They constitute a subtype, per se, with particular clinical and histological characteristics and a worse prognosis.

#### 21.5.6.1

##### *Electron Microscopy and Immunohistochemistry*

Tumor cells are extremely variable in dimension and shape [1059, 513, 1981, 3546, 2217]. Common and constant characteristics are the extreme richness in cytoplasmic organelles, the presence of complex junctional apparatuses, and the abundance of tonofilaments. The cells possess notable quantities of glycogen, osmiophilic secretory granules and lipid inclusions. The smooth and the rough endoplasmic reticulum and the Golgi apparatus are well developed, and there is a large number of mitochondria. Microtubules are occasionally found. The nuclei sometimes present invaginations of the envelope, while the chromatin is mostly arranged peripherally.

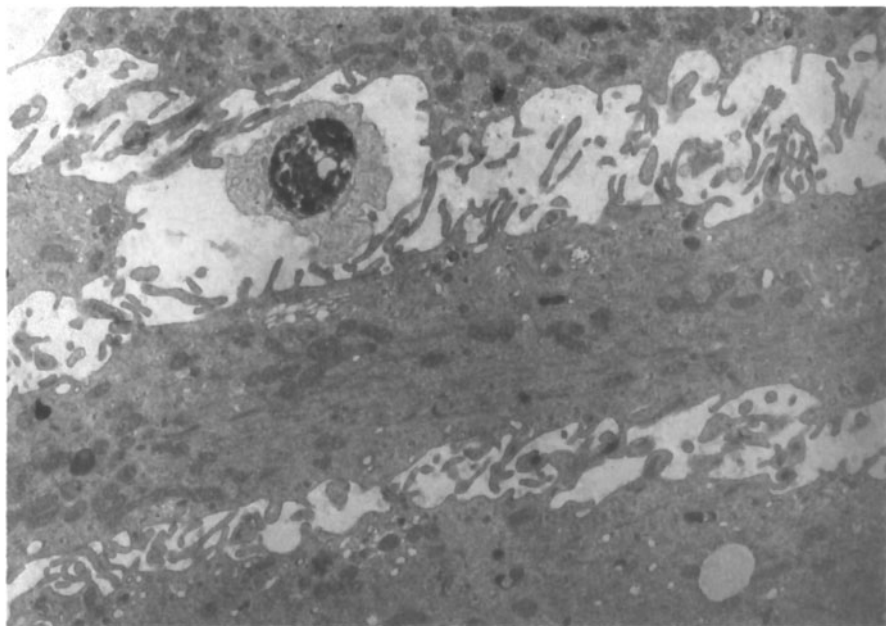


Fig. 21.22. Microvilli and "prickle" cells. Uranyl acetate, lead citrate stain,  $\times 40000$

The cell surface is provided, especially in the central part of the trellises, with numerous microvilli among cells of polyhedral aspect ("prickle cells") (Fig. 21.22). The microvilli of juxtaposed cells delimit extracellular spaces of variable amplitude, sometimes with a microcystic appearance. Two types of intercellular junctions can be recognized: Tight junctions and desmosomes formed by a thickening of juxtaposed membranes about 400 nm in length and 30–40 nm wide. Bundles of short and poorly developed 50- to 70-Å tonofilaments frequently project on desmosomes (Fig. 21.23). Bundled or scattered tonofilaments may also be seen in the cytoplasm, especially in maturing epithelial cells sited in the center of the trellises. The cells at the periphery, with a lesser number of tonofilaments, have a cylindrical shape and rest in a single layer on a basement membrane outside which connective tissue or cystic spaces are found. The nuclei are oriented perpendicularly to the basement membrane. These cells have hemidesmosomes toward the basement membrane and develop complete desmosomes between each other. A large number of desmosomes and interdigitations between the cytoplasmic processes are visible between cells situated immediately internally to the cylindrical cells.

Stellate cells in the center of the epithelial nests, loosely arranged and elongated, show the same ultrastructural features. They are rich in tonofilaments and desmosome type junctions among the long and thin cytoplasmic processes, which sometimes delimit more or less large cystic spaces. The stellate cells derive from a regression of polygonal cells due to the marked expansion of the surrounding extracellular spaces [1059]. Their resemblance to cells of adamantinomas and ameloblastomas of the mandible has already been emphasized [1059].



Fig. 21.23. Tonofilament and desmosomes. Uranyl acetate, lead citrate stain,  $\times 40\,000$

A finely reticular material, different from that of the basement membranes delimiting some cysts, is observed along the cytoplasmic membrane of stellate cells, close to the cyst lumen [909]. Analogous material has been found in some superficial epithelia including squamous cells of the skin undergoing keratinization.

Keratinization has been discussed for a long time from the histochemical point of view, as related to the presence of acid mucopolysaccharides, sulfhydrylic groups, and sulfur bridges [936]. Keratohyaline granules have also been described in the cytoplasm of some cells with light microscopy study [1059, 2627]. Some authors [3441, 3801], however, deny the existence of the keratinization process, rather characteristic of the so-called suprasellar epidermoid cysts, with which craniopharyngiomas have been confused [2902]. A possible distinction between craniopharyngiomas and epidermoid cysts, however, [2627] would not be based on the presence of keratin, but on the finding of adamantinomatous areas, which are lacking in epidermoid cysts. In the absence of such areas, the only differential criteria are the “greater tendency” to stratification and keratinization shown by epidermoid cysts.

Ultrastructurally, the tonofilament masses represent the molecular substrate of keratohyalin [513, 1060, 1858, 1981, 3546, 2217, 2956]. The cells situated in the center of the epithelial trellises show “massive fibrillary hyperplasia” [513] and degenerate. The tonofilament bundles become extremely thickened (up to 200 nm) and are arranged without order in the cytoplasm. When the cells die, the masses of tonofilaments take up the features of electron-dense bodies corresponding to the keratohyalin granules seen under light microscopy. The debris of disintegrated cytoplasmic organelles participates in the process [513]. The process of keratinization in

craniopharyngiomas is different from the analogous process in the epidermis, only because it does not occur in an orderly manner [1059].

Antibodies to keratin have confirmed immunohistochemically the presence of cytokeratin in craniopharyngioma, in the cytoplasm of both squamous and stellate cells. A positive reaction was also observed in squamous cell nests in the pars tuberalis of the normal hypophysis and in the cylindrical cells delimiting the intrasellar microcysts of the pars intermedia (Rathke's cleft cysts). On the contrary, the cells of the normal and tumor adenohypophysis and tissues of neuroectodermal derivation did not react. It should be remembered that in a normal and a tumor hypophysis, microfilaments, but not tonofilaments, can be demonstrated [1764].

#### 21.5.6.2

##### *Calcification*

Closely correlated with keratinization is the process of calcification. It is a frequent occurrence and a point of distinction from adamantinomas of the jaw [1059]. Its incidence is very high, up to 75% of cases in series comprising only adult cases [2627] and even higher in series including children [1569]. It can be so marked as to be seen on a plain skull X-ray.

Microscopically, it more often involves adamantinomatous areas (35%) but may also be found in squamous areas (15%), in the stroma (13%), and in the surrounding neural parenchyma (11%) [2627]. The histological type, typical of adults [1569] and considered of metaplastic origin, does not contain calcifications and keratin. Both characteristics are also absent in the papillary variant [1067].

Investigation by X-ray microanalysis [3546] has demonstrated that the calcified areas contain Mg, P, and Ca, with the greatest peak for P. Diffraction studies have demonstrated that the Ca is present as hydroxyapatite crystals [1858]. In general, the calcification process takes place in areas in which masses of keratin are demonstrable [2902]. Under the electron microscope, calcium deposits are found in proximity to such masses but also in intact cells [1059] or in cystic spaces apparently devoid of keratin [1059, 2217]. The calcium aggregates recall the morphology of hydroxyapatite crystals of bone.

The genesis of the calcification process has been documented ultrastructurally [1858, 2956]. The cells undergoing keratinous degeneration lose their complement of organelles, the cytoplasmic membrane, and often also the nucleus. In the cytoplasm, needle-shaped apatite crystals become demonstrable among the tonofilaments and within vesicles lined by a 150- to 500-nm membrane. The vesicles, perhaps degenerated mitochondria, are the primary focus of deposit of the hydroxyapatite crystals, analogous to what is observed in the formation of psammomatous bodies in meningiomas [1976]. The coalescence of vesicles and calcified tonofilaments leads to the formation of large, calcified bodies. The tonofilaments are likely to orient the precipitation of the hydroxyapatite crystals. The process of calcification may extend in some cases to the production of true lamellar bone [2902].

### 21.5.6.3

#### *Cystic Component*

The cystic component of craniopharyngioma may prevail, and the solid part can be confined to a small intracystic node.

The cysts may be subdivided into three varieties according to the lining cellular component. Stromal cysts are more often of microcystic type and contain eosinophilic clots and sometimes aggregates of foamy cells (Fig. 21.24). They are recognized ultrastructurally by the basal columnar cell lining with a continuous basement membrane on the luminal side. Such cells are considered to correspond to the cells of the germinal layer of the epidermis [1059].

In loose adamantinomatous areas, microcysts derive from the coalescence of small, extracellular, dilated spaces. Also, the cells delimiting the cyst are of the basal columnar type, but the basement membrane is situated on the side opposite to the lumen. The cells have long processes connected by junctional complexes [1059, 3546] and are often covered, on the luminal side, by the reticular material described previously. A third type of cyst, also affecting the epithelial component, originates from the maturation and subsequent exfoliation of degenerated squamous cells (Fig. 21.25a). These cysts are delimited by a stratified squamous epithelium and often contain keratin debris and calcium deposits. Ultrastructurally, the squamous cells of the luminal rim show numerous microvilli [1059, 3546] and are occasionally covered by a rim of keratin [1059].

The microcysts mostly belong to adamantinomatous areas, and the cysts of large dimension may be lined by squamous epithelium and only rarely by stellate cells [2902]. More frequently, however, the macrocysts are lined by various cell types at the same time, sometimes demonstrating transitional forms between squamous and adamantinomatous elements [2627]. The cysts in adamantinomatous areas and those resulting from maturation have been examined under the scanning electron microscope [3546]. Microvilli were easily visible in both. Stellate cells often showed numerous vesicular processes on the luminal surface, indicating exocytosis or pre-keratinization.

The stromal component of the craniopharyngioma is discretely vascularized, and, apart from microcysts, it is also the site of regressive changes such as myxoid degeneration and calcifications [2627, 2871, 2902, 3801].

Stromal microcysts are due to local vascular changes with consequent colliquative necrosis and also extravasation of proteins and fluid because of the increased capillary permeability. Ultrastructural investigations have demonstrated numerous capillary abnormalities [1328, 2217, 3546]. Capillaries are immersed in an extracellular matrix rich in collagen, and the basement membrane is often reduplicated. The endothelial cells contain pinocytotic vesicles, filaments, microtubules, and often Weibel–Palade bodies [1328]. The intercellular junctions are well developed; however, they do not give rise to “tight junctions” [2217].

Fenestrations formed by small 50-nm pores, which favor the exit of liquids and proteins to the extravasal spaces, are frequently observed. The fenestrated capillaries could arise from a proliferation of blood vessels originating from adjacent sites like the hypophysis and hypothalamus whose system of capillaries has fenestrae [2217]. Alternatively, they are characteristic of the tumor, on the basis of the finding of fenestrated capillaries in tissues similar to craniopharyngioma, like the skin [1328].

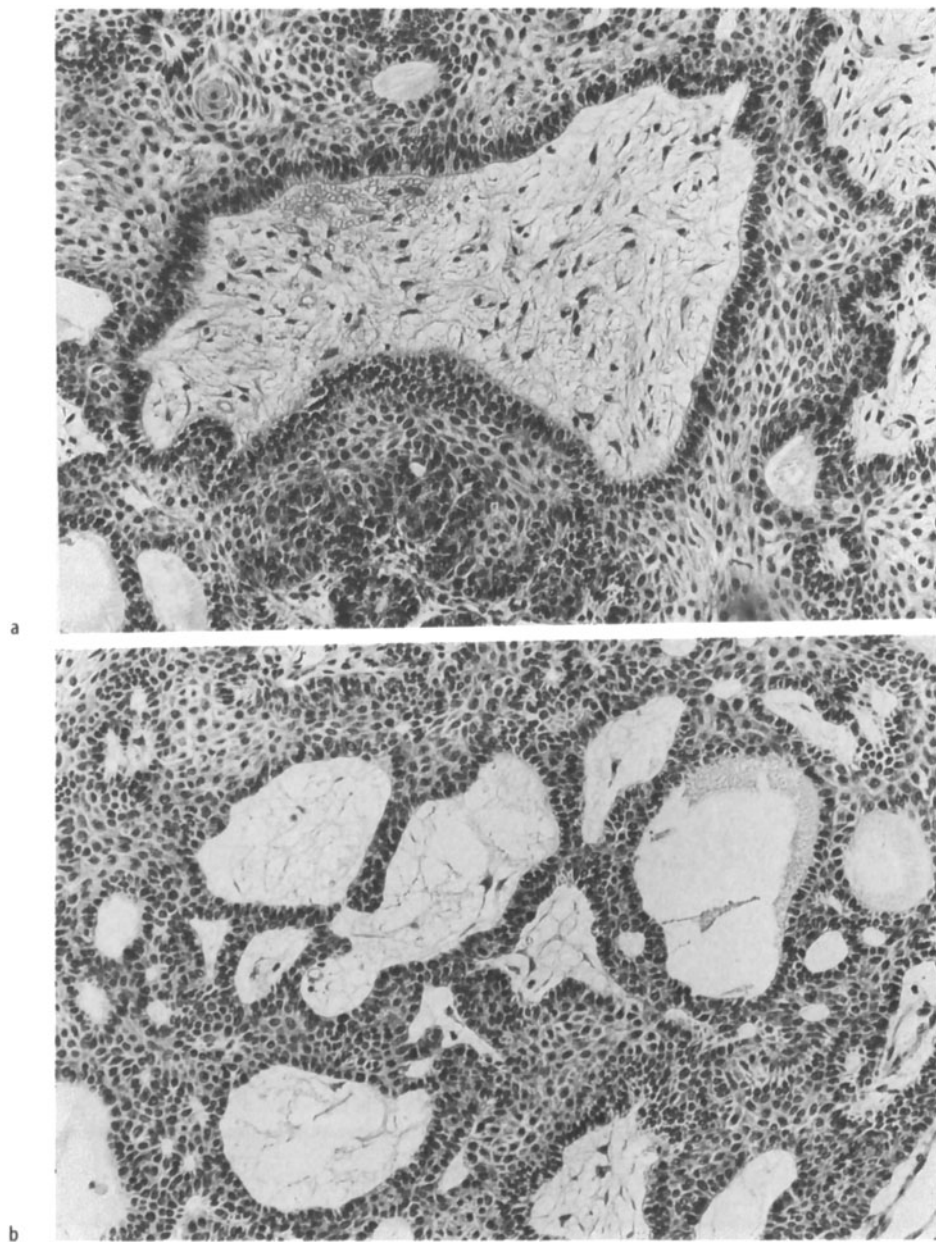
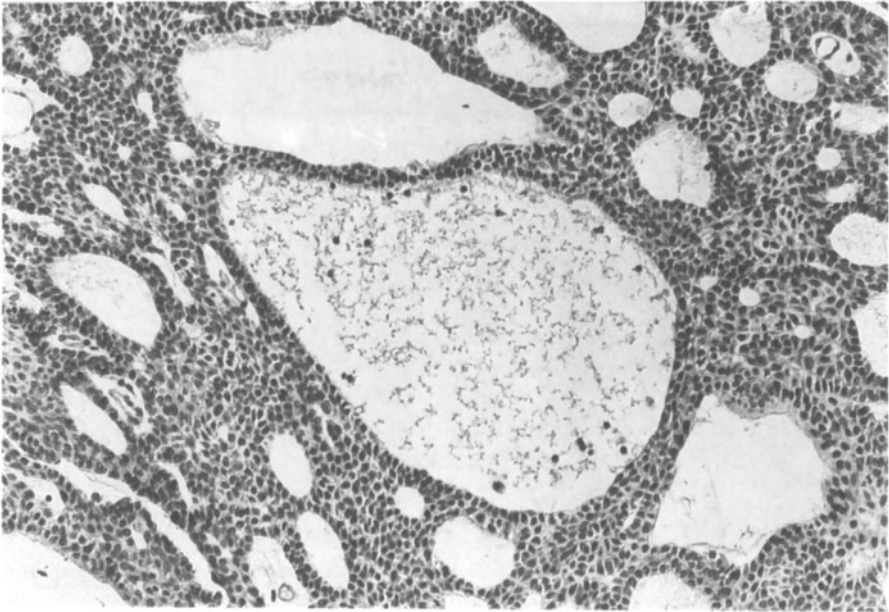
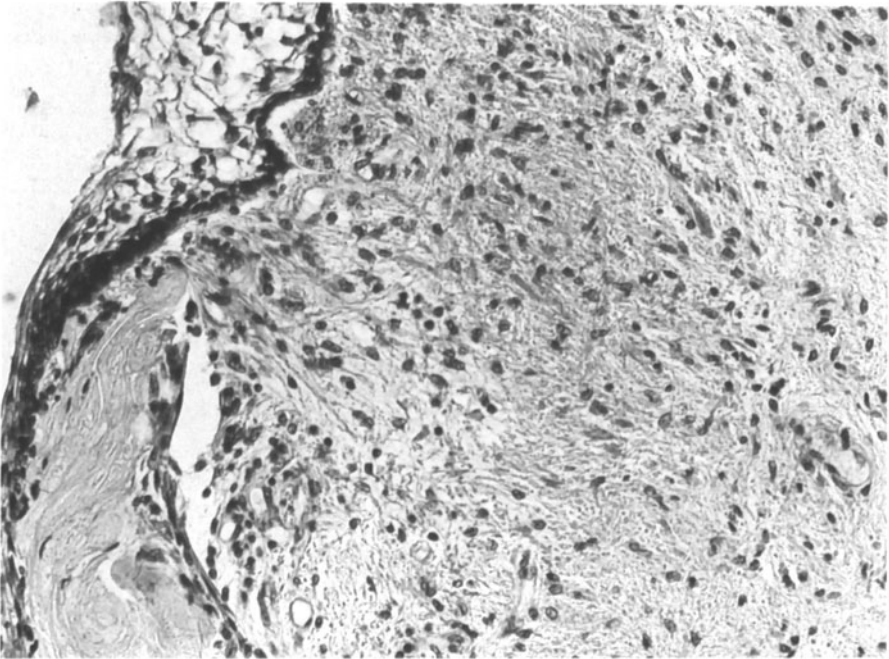


Fig. 21.24a,b. Craniopharyngioma, stromal cysts in evolution from a to b. H&E,  $\times 300$



a



b

**Fig. 21.25a,b.** Craniopharyngioma. **a** Epithelial cyst. H&E,  $\times 300$ . **b** Reactive gliosis with Rosenthal's fibers around the tumor. H&E,  $\times 200$



### 21.5.7

#### Adjacent Tissue

Although the tumor is circumscribed and occasionally shows an apparent capsule, numerous adhesions with blood vessels, cranial nerves, or the arachnoid-pial surface of the brain are present. The relationships between tumor and brain parenchyma vary in the different patterns. Sometimes, the tumor grows in association with cerebral tissue without compressing or eliciting any reaction. In these cases, the neural tissue surrounding the tumor appears malformed and constituted of bundles and streams of small glial cells, like those seen in other precocious congenital malformations [1569]. More often, however, the neural parenchyma is compressed or the site of an intense fibrillary reactive gliosis. A subependymal astrocytic reaction has also been described in rare cases of craniopharyngioma with intraventricular growth [1126, 3054]. The fibrillary gliosis is often associated with numerous Rosenthal's fibers (Fig. 21.25b) [3801, 2871, 2902], similar to those seen in cerebellar astrocytomas [1059]. Inflammatory cells, lymphocytic infiltrates, and foreign-body-type giant cells may be observed within the tumor and in the adjacent cerebral parenchyma [3801, 1569, 2627, 2902]. Both gliosis and chronic inflammation have been related to the release of keratin and cholesterol from the tumor [1981, 2627]. Even though the cholesterol is produced by a mechanism of cellular degeneration and subsequent colliquation, *in vitro* observations demonstrated that it is actively produced from viable cells of the tumor [1981]. Similarly, in tumors produced by intracerebral implantation of oral epithelium in the rat, an accumulation of cholesterol crystals was observed at the viable periphery of the tumor and not in the necrotic center [3512]. An increased cholesterol production has been found *in vitro* in cultures of craniopharyngioma which featured an aggressive behavior both *in vivo* and *in vitro* [1981].

An aggressive clinical behavior with a tendency to invasiveness and local infiltration has been repeatedly stressed [1178, 2871, 3582]. This is in part due to the impossibility of a radical surgical extirpation due to the location of the tumor. However, the growth of small prongs of neoplastic tissue (Fig. 21.26) within intensely gliotic areas, which in the past were erroneously attributed to carcinomatous degeneration [2902], may impede total removal and be responsible for recurrences [1059, 2217].

Although malignant degeneration has never been observed in the prongs [2871, 2902], atypical features have sometimes been identified at the ultrastructural level [1981].

### 21.5.8

#### Relationships of Craniopharyngiomas with Rathke's Fissure Cysts

Recently, cases of suprasellar craniopharyngioma have been described in which some cuboidal and columnar cells featured well developed cilia or vacuoles filled with PAS-positive material [2166, 1138]. In one case, squamous and columnar cells were resting on the same basement membrane and showed transitional features between the two types [2166]. Furthermore, two different histological features in dumbbell craniopharyngiomas have been described [2902]: The suprasellar portion was formed by typical squamous elements and the intrasellar one by a cuboidal or

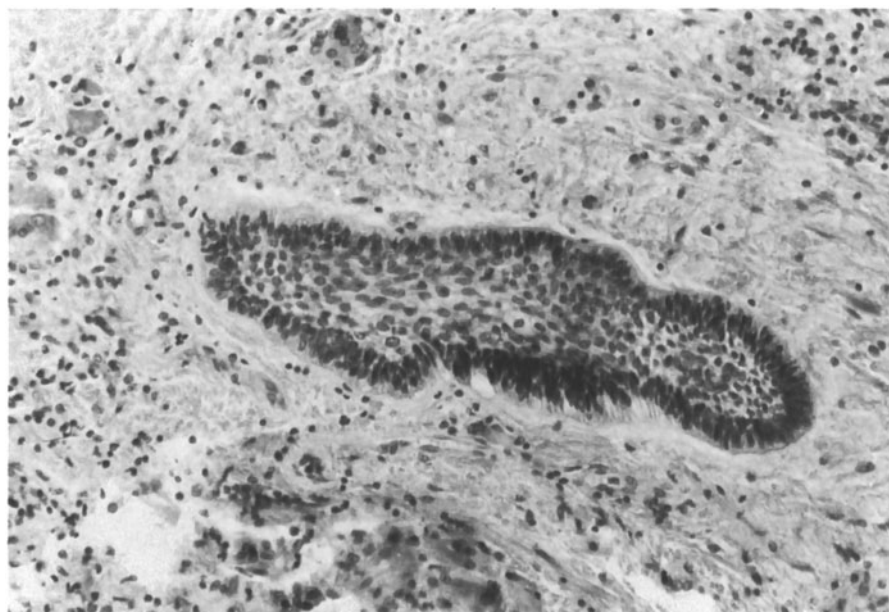


Fig. 21.26. Craniopharyngioma, prong of epithelial tissue in an area of gliosis. H&E,  $\times 300$

ciliated epithelium. The importance of these observations derives from the fact that analogous features (cylindrical ciliated cells and mucin secretory granules) are characteristic of the so-called Rathke's cleft cyst [176, 3133, 219, 3754, 1640, 3540, 729, 730]. As has been said in the embryogenetic section, it is thought that intrasellar residua of Rathke's pouch, occasionally found only postmortem (13%–22% of all autopsies), may give rise to small cysts or to structures like glands between the anterior and intermediate lobe of the hypophysis [730, 1138, 2902]. Very rarely, the cysts may become symptomatic, as in 63 cases reported up to 1982 [3300]. Likely, in these cases, the cellular residua start again to proliferate and form cysts filled with mucin. The expansion of the cyst, usually intrasellar, but with suprasellar extension in a third of cases [2863], may cause hypopituitarism, compression of chiasm, obstructive hydrocephalus, and sometimes the "empty sella" [1087, 3754, 139, 3540, 1729, 3300, 2374, 2863]. The finding of completely suprasellar cysts is very rare [2863, 2902]. These cases can be distinguished from craniopharyngioma even on macroscopic grounds because their content is fluid and mucinous and not of the "machine oil type."

In the majority of cases described, the histological appearance is constant: The cyst wall is composed of a single layer of cuboidal or ciliated columnar epithelium containing signet ring cells and resting on a basement membrane (Fig. 21.27a). The cells have cilia with a typical 9+2 microtubular arrangement, microvilli, and junctional complexes of ependymal type [729]. PAS- and mucicarmine-positive material is present both within cells and in the cystic cavity [1138]. Calcifications are mostly absent [3754, 2863], with exceptions [1138]. Keratin and cholesterol deposits are also lacking. The wall may contain chronic inflammatory cells [139, 2863]. In one case,

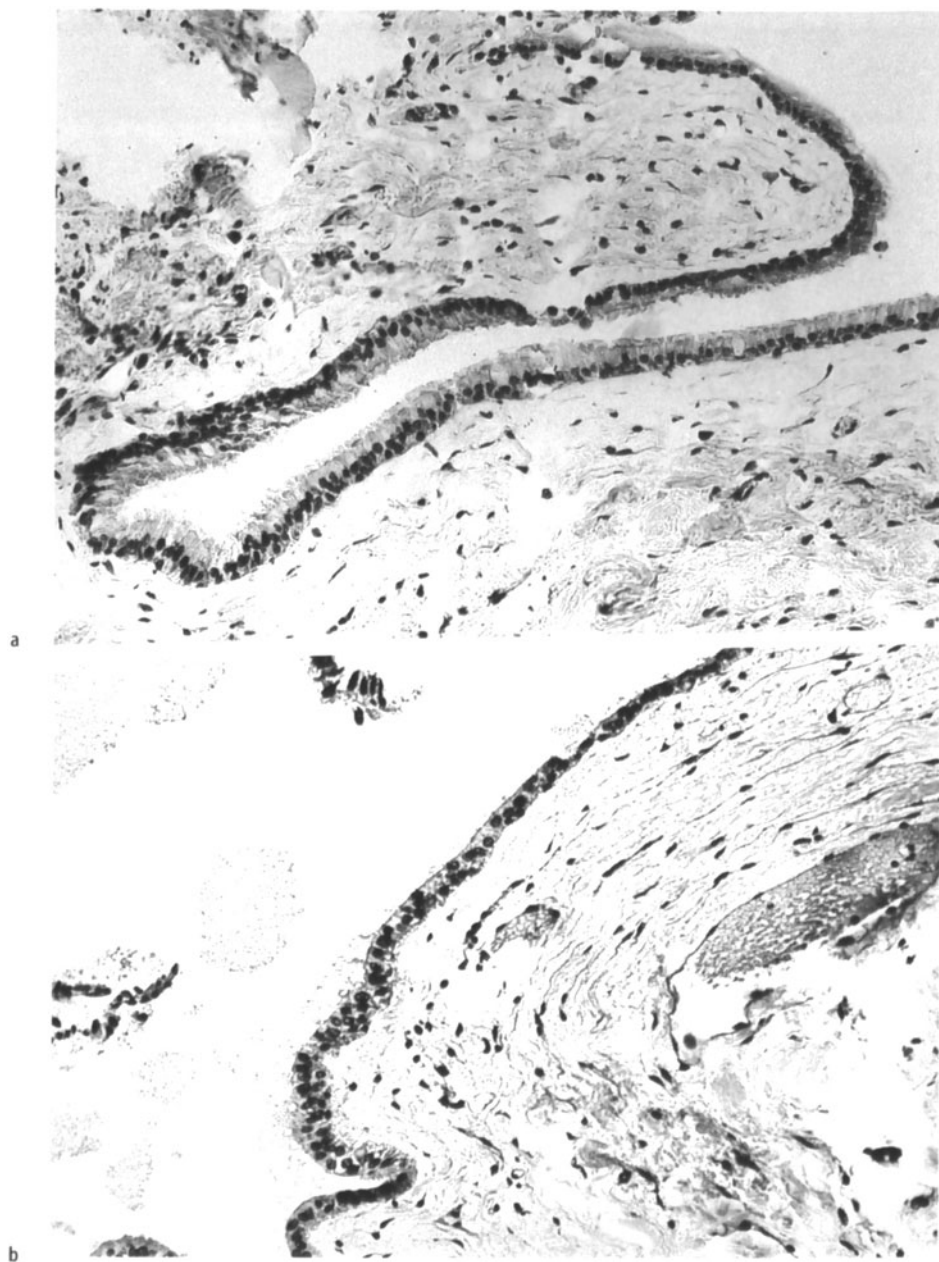


Fig. 21.27. a Rathke's pouch cyst. b Colloid cyst, columnar epithelium. H&E,  $\times 300$

amyloid has been demonstrated in the stroma underlying the basement membrane, likely due to the presence of peptides released by the compressed hypophysis [555].

Beside these frequent aspects, numerous histological variants have been reported, often within the same cyst. The epithelium may be simple columnar or pseudostratified, cuboidal, cylindrical with or without cilia, or vacuolated and may form papillae with intraluminal projections or intraparietal gland-like structures [3184, 729, 1138].

Rarely, isolated foci of squamous cells with keratinization, ultrastructurally identical to the analogous cells of craniopharyngioma [3754, 1728, 729], have been described [3184, 3754, 1640, 3540, 729, 1138]. The ultrastructural study of cells from a cyst in culture has furthermore revealed cellular elements with transitional characteristics between squamous cells and cylindric cells, either ciliated or containing secretory granules [3754].

If, then, in their more typical histological aspects, craniopharyngiomas and cysts of Rathke's cleft may be easily differentiated, it should be remembered that the distinction between the two lesions is important because of their different clinical behavior. In contrast to craniopharyngiomas, Rathke's cleft cysts do not have an invasive appearance, do not recur, and can be surgically treated by simple drainage and opening of the wall [555, 729]. In mixed cases, it is, therefore, important to evaluate the predominant epithelial type before attributing the tumor to one of the two types. It has been reported that symptomatic cysts of Rathke's cleft containing squamous epithelium have a more aggressive behavior, tend to recur, and behave, in practice, like craniopharyngiomas [2863].

The existence of cases with intermediate characteristics between craniopharyngiomas and Rathke's cleft cysts is considered in general as an index of the common embryological origin from remnants of the epithelium of the stomodeum [2902, 1372, 1373, 3754]. However, histological findings typical of Rathke's cleft cysts, i.e., cilia, mucin, and acid mucopolysaccharides, may also be found within neuroepithelial structures (choroid and ependymal epithelium) [3184, 729]. A mixed origin for the cellular elements of the cysts, beginning with neuroepithelial residues for columnar epithelium and with residues of the epithelium of the stomodeum for the squamous elements, has therefore been proposed [729, 730]. As an alternative, the squamous component could have a metaplastic origin from the cuboidal or columnar epithelium [2902].

The possible origin from the neuroepithelium is confirmed by the histological similarity of these cysts with colloid cysts of the third ventricle. These structures, which are today mostly considered as nonexclusive of the third ventricle and with a possible manifestation on the midline along the whole neuraxis [3183, 1327, 1060, 3185, 18, 1212], would then be different from Rathke's pouch cysts only for the exclusively ventricular situation.

The origin of colloid cysts themselves is still hotly debated. The classic view is that they are of neuroepithelial origin [3183, 2902, 729]; however, analogies with the epithelium on the basis of ultrastructural findings have been observed [1328, 1060, 1326, 1057, 2316, 3740, 1212], as well as the presence of various cellular types, columnar, ciliated, columnar nonciliated, stratified squamous. Squamous cells of colloid cysts furthermore possess tonofilaments [1057] and tight junctions of the macula adherens type which are not characteristic of the neuroepithelium and are found instead in cysts of Rathke's cleft and in craniopharyngiomas.

A recent review of 19 cases has established that Rathke's cleft cysts, neuroepithelial cysts, craniopharyngiomas, and epidermoid and dermoid cysts all appear to arise from ectoderm and are distributed along a common spectrum with variable differentiation [1247].

On the basis of the histological findings, craniopharyngioma, Rathke's cleft cysts, and colloid cysts of the third ventricle could have a common embryological origin from the epithelium of the primitive stomodeum. The three neoplasias may therefore be framed in a "continuum," differing from each other on the preponderance of a certain cellular type and on their anatomical location.

### 21.5.9

#### Prognosis, Treatment

The choice of the optimal therapeutic approach for craniopharyngioma is still very controversial. Three choices have been put forward: surgery, radiotherapy, and chemotherapy. The evaluation of the results of treatment from the literature is not straightforward for two reasons: (1) the follow-up period is often too limited and (2) series based on more than one therapeutic protocol are very rare.

The need for surgical intervention is universally recognized; however, the general strategy of treatment is still controversial [2937, 512, 2712]. There is disagreement with respect to the extent of surgery. The "radical" operation offers, on average, 80% long term control of the neoplasm [2152, 1611, 3353, 1366, 3139, 56, 2217, 3358]. Recurrences are usually observed within 2 years [441]. However, there are reports of recurrences after some decades from an operation which was otherwise judged to be radical [1569]. The best results are obtained with noncalcified tumors with a diameter under 3 cm [3139].

The radical operation is criticized by various authors [2627, 2317, 409, 3438, 441, 905, 2085] because of the subsequent severe neurological and endocrine damage. It has, however, to be remarked that the same histological characteristics of the tumor, with the formation of prongs in the surrounding neural parenchyma and the absence of a limiting capsule, renders the term "radical" improper [441]. In the Toronto group's experience, over 60% of craniopharyngiomas in childhood can be totally resected with minimal significant morbidity and mortality [1368]. Radical surgery is recommended by the vast majority of pediatric neurosurgeons [2944]. On the other hand, subtotal removal alone is not useful in the control of the tumor: The survival at 5 and 10 years is 34.9% and 27.1%, respectively [2085]. These figures notably improve if subtotal removal is associated with radiotherapy [2627, 56, 2317, 409, 3438, 441, 905, 2085], and in this event it becomes 89% and 76%, and the incidence of recurrence at 10 years is below 25% [441]. In a series of 37 children [906], failures after total removal were 57% versus 7% in patients undergoing more conservative surgery. In series including only adult cases, however, the 5-year survival after subtotal removal and radiotherapy is only 50% [2627]. Though craniopharyngioma is a theoretically radioresistant tumor [409, 3371], the results given above demonstrate the efficacy of radiation treatment. Some authors have proposed associating radiotherapy with the most conservative surgical treatment so as to limit the damage to the hypothalamus and optic tracts [2317, 3438]. It is thought that the main effect of irradiation

tion is to decrease the amount of fluid within the cyst [1366]; however, there are histological data which demonstrate the total destruction of the tumor after radiotherapy [1770, 56]. The doses usually employed are around 5000–6000 rads, with fractionation (200 rads/day). There appear to be no differences in the survival figures in relation to the histological type [1746].

Radiotherapy itself is not, however, immune from possible negative effects. There are reports of mineralization of the basal ganglia, frontal lobes, and hypothalamus [905], late necrosis, and occlusive angiopathy [56, 2317, 905]. The development of astrocytomas [3253] and of meningiomas [2317] has also been described. Within the confines of radiation therapy for craniopharyngiomas with a marked cystic component, endocavitary irradiation (brachytherapy) by means of various types of isotopes ( $^{32}\text{P}$ ,  $^{198}\text{Au}$ ,  $^{90}\text{Y}$ ,  $^{186}\text{Re}$ ) has been proposed [1729, 2367]. The dose at the wall is 30 000–40 000 rads. In both series, the follow-up demonstrated obliteration of the cysts.

From all these experiences, it can be deduced that the best results are obtained by total surgical removal; however, the larger the tumor, the greater is the damage to intracranial structures. On the other hand, radiotherapy may lead to other damage to the nervous structures. The only solution is to remove the tumor surgically when it is still small, that is after an early diagnosis. It must be taken into account that the clinical features of adamantinous and squamous papillary tumors are different in adults and children [11].

The intratumor injection of bleomycin during operation has been proposed as an alternative to radiotherapy [3371]. Such a drug has in fact been demonstrated to be very efficacious in the therapy of squamous cell carcinomas, especially in cystic tumors.

Brachytherapy for cysts and radiosurgery have been proposed, with controversial results [120, 3501].

## 21.6 Neuroepithelial and Non-Neuroepithelial Cysts

### 21.6.1 Colloid Cysts of the Third Ventricle

These lesions also go under the name of neuroepithelial or parapyseal cysts, as it is generally thought that they originate from the paraphysis. This structure has the appearance of a racemose gland, is present in the human embryo measuring from 17 to 100 mm, and then disappears. At the same time, the diencephalic ependymal pouches develop, and both these and the parapyseal pouch may become isolated as closed vesicles and give rise to colloid cysts. This interpretation is valid for the colloid cysts of the anterior part of the third ventricle. Although this is the most frequent and most important location, neuroepithelial cysts have also been found elsewhere, for example, in the fourth ventricle and in the lateral ventricles. Six cases from the literature plus a personal case have been reviewed [678].

Not everyone agrees that the cysts originate from the paraphysis. Some authors believe that they originate from the choroid plexus [1273] or from the plexus and ependyma [3183]. According to some, the origin of the third ventricle cysts are iden-

tical to that of cysts of the lateral ventricles, only the location is different [678]. They arise from an embryonal ependymal diverticulum as telencephalic or diencephalic cysts. Actually, they develop because of folding of the neuroepithelium in or outside the ventricle and, therefore, could originate wherever there is an ependymal lining. In relation to the third ventricle, these authors maintain that the cysts arise from the paraphysis, which is nothing else but the choroid plexus [3181].

#### 21.6.1.1

##### *Frequency, Age, Site*

Colloid cysts of the third ventricle are more frequent in pathological than in neurosurgical series. In autopsy material, cysts were found in more than 50%, 66.2%, and 50% of telencephalic, diencephalic, and myelencephalic plexuses, respectively [792, 3181]. However, the majority of these cysts are asymptomatic. They represent 0.5% of all brain tumors [1446], are very rare in infancy and appear prevalently in males. Adults are more usually affected.

Neuroepithelial cysts may originate at all sites at which neuroepithelium normally exists. The literature has numerous reports of cysts with diverse locations, even in the cauda equina [2311]. However, as has already been said, those of the third ventricle may have a particular clinical importance.

#### 21.6.1.2

##### *Macroscopic Appearance*

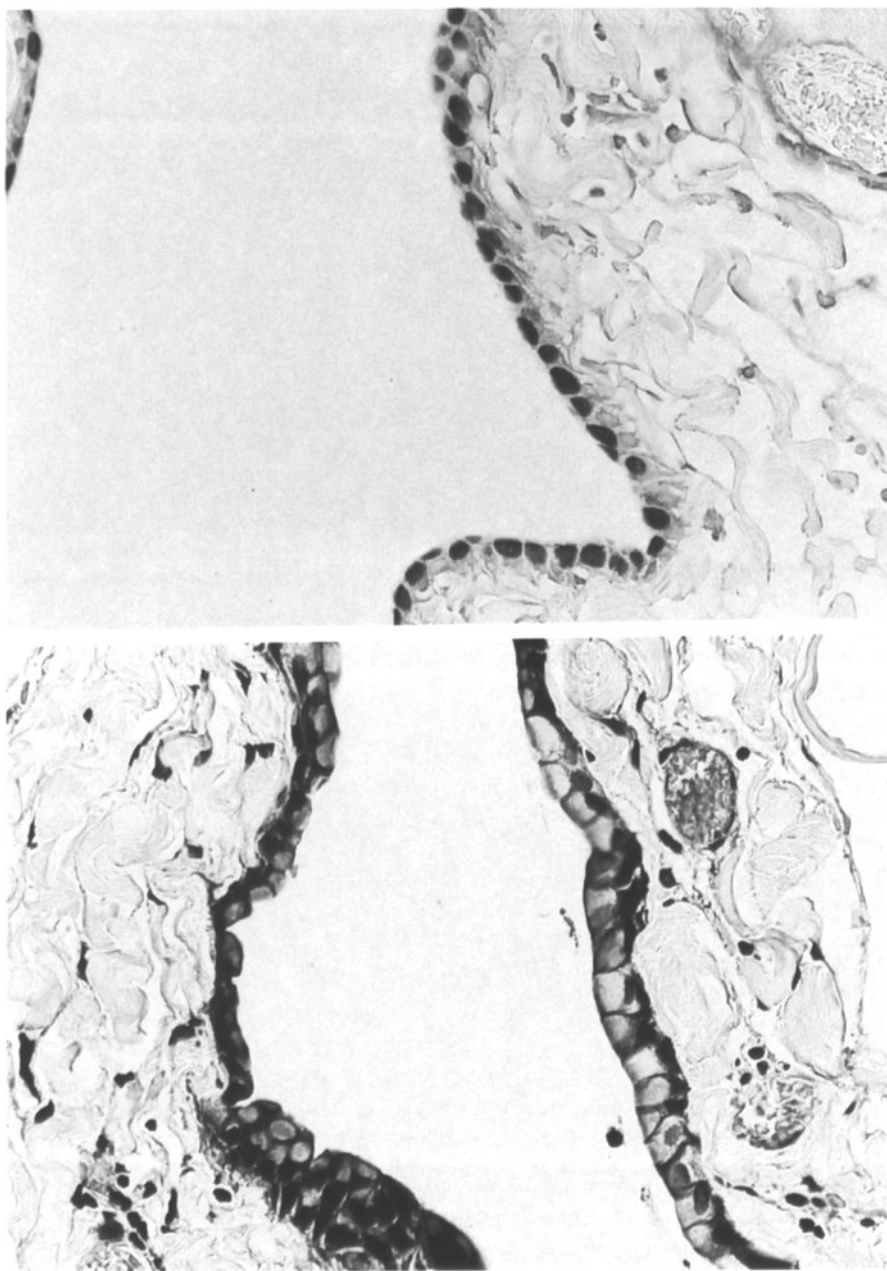
The cysts are spherical, of various dimensions and strongly adherent to the surrounding tissue. In the third ventricle, they adhere to the stroma of the choroid plexus in correspondence to the foramen of Monro. The content is usually dense and hyaline.

#### 21.6.1.3

##### *Microscopic Appearance*

The cyst is usually lined by an often ciliated, cuboidal or columnar epithelium (Fig. 21.27b). Sometimes, however, the epithelium may be lacking. The content of the cyst is PAS and mucicarmine positive. A similar reactivity, but in small droplets, has been found in the cytoplasm of cells lining the cysts [2335, 3181], as may be observed in the choroid plexus and in the ependyma [3181].

Under the electron microscope, the cyst epithelium has been demonstrated to be of ependymal type [2047, 3411]. In a case report [587], the epithelium was formed by cells of two types. In some areas, these were cuboidal or columnar, intermittently adherent to each other by means of "apical bars." The intercellular spaces were filled with a proteinaceous fluid, and the cytoplasm was rich in organelles. In other areas, instead, the cells were ciliated and contained abundant mitochondria and cilia. These had the usual 9+2 tubular arrangement, while others were abnormal.



**Fig. 21.28a,b.** Spinal enterogenous cyst. **a** Periodic acid-Schiff (PAS)-positive goblets. PAS-hematoxylin,  $\times 400$ . **b** Positivity for cyokeratin. PAP-DAB,  $\times 400$



### 21.6.2

#### Spinal Enterogenous Cysts

These cysts are lined with columnar, intestinal-type epithelium (Fig. 21.28) and are located in the spinal canal, usually but not always in an extramedullary situation [1240].

They may be intra- or extradural [19], and they are usually situated in the cervical and dorsal segments. The lining epithelium is columnar and PAS positive, sometimes formed by goblet cells containing mucus, or sometimes featuring foci of squamous hyperplasia [2871, 2165].

The origin of these cysts has been much discussed. According to some, they are similar to gastroesophageal cysts, and this would be supported by the existence of simultaneous vertebral anomalies. According to others, instead, their pathogenesis would have to be considered together with that of Rathke's pouch cysts and with that of colloid cysts of the third ventricle.

### 21.6.3

#### Arachnoid Cysts

The characteristics of these cysts are a thin wall and a situation between the inner layer of the dura and the arachnoid membrane. They contain a clear and colorless or xanthochromic and strongly proteinaceous fluid, are relatively frequent, both in adults and children, and are found mainly in the Sylvian fissure, in the cerebellopontine angle, along the midline in the posterior fossa, or in the cerebellar hemispheres. In the spinal cord, they may be both epidural and subdural, are posteriorly situated in relation to the dorsal nerve roots, and may be multiple [400]. The wall is formed by a collagenous membrane covered by arachnoid cells. The adjacent neural tissue may sometimes appear atrophic and gliotic.

The origin of arachnoid cysts is variable. They may result as a consequence of episodes of leptomeningitis or following trauma, even at birth, or be of malformative origin [2766]. They may be clinically silent or may become large and cause hydrocephalus.

## 21.7

### Lipomas

Craniospinal lipomas belong to the group of rare tumors of the nervous system. Nevertheless, since the last century they have raised notable interest because of their origin, which is still being debated at present.

Virchow [3555] considered lipomas the result of hyperplasia of adiposomeningeal cells, whereas for Gowers [1148] they represented a degenerative process of neural structures. Bostroem [314] put them into the same group as dermo-epidermoid cysts derived from a dysembryogenetic defect, characterized by remnants of adipose cells of embryonal type. Of the same opinion later were others [3539] who connected lipomas with the persistence of meningeal embryonal mesenchyme. Subsequently,

Scherer [2981], followed by others, took up and developed this hypothesis and thought that lipomas derived from the primitive embryonal mesenchyme as a result of the transformation of multipotent cells present around the capillaries. Because the mesenchyme of both mesodermic and ectodermic origin participates in the anlage of the leptomeninges, the idea that lipomas had to be considered as hamartoblastomatous processes of ectodermal origin [804] was also put forward. It has been observed that lipomas, which develop some time after gastrulation, contain only adipose tissue, whilst those which arise immediately after are characterized by the presence of mesodermal derivatives such as bone. Lastly, those related to a disturbance which occurred before or during gastrulation feature neuroectodermal elements in addition to mesodermal ones [3577].

In favor of the dysontogenetic concept of the origin of these tumors are their topography and their frequent association with dysraphic anomalies and various malformations. For example, the concomitant presence of pes cavus [161], of subcutaneous lipomas at the site corresponding to the spinal lipoma [804, 1002], of a pilonidal sinus [370], of spina bifida, of osseous defects and meningocele [3781, 2816] have been described.

Despite the fact that the dysembryogenetic concept is today accepted by the majority of researchers, a classification on an embryological basis does not appear sufficiently documented. However, from the practical point of view, it is useful to subdivide these tumors according to a topographic criteria into cranial and spinal, midline and lateral, intradural and extradural [3317]. There are elective locations, such as the corpus callosum, which form the majority of cases in various series.

### 21.7.1

#### Frequency, Age, Site

Lipomas are rare even if not exceptional tumors. They represented no more than 0.5% of all intracranial tumors in the collection of Bailey [128]. Only four intracranial lipomas were found in a series of 5000 autopsies [3577]. Thirteen cases have been reported [372].

The lesions are seen most often in the corpus callosum [1297, 3801, 3781], and they are frequently associated with dysraphic abnormalities [1625]. Other reported sites include the infundibulum, quadrigeminal plate (especially its caudal part), choroid plexuses of the lateral and third ventricles, basal and convexity cisterns, spinal cord (extending from a few to several segments, especially in relation to the posterior funiculi [1768, 2981, 3799, 990, 1226, 371, 1625]). Recently, two lipomas localized in the mesencephalic tectum and rostral pons, associated with Pickwick's syndrome, have been reported [3160]. Extradural lipomas are more frequent in the middle and lower thoracic segments, while the intradural ones are located at the upper thoracic, cervical and conus-cauda equina level [1085, 2639].

The age of occurrence is difficult to establish, because they may appear in the young and in patients of middle age, but may also be found incidentally at autopsy. On the other hand, in the literature, some lipomas in the senile [2060, 3741] and infantile age group [2899] have been reported.

Both sexes are equally affected.

### 21.7.2

#### Macroscopic Appearance

They have a roundish or flattened, variable shape adapted to the site at which they are located and are of different sizes, from that of a pea to voluminous masses. Generally, they are translucent in appearance, yellow, soft-fattish in consistency and are demarcated from the surrounding tissue by a connective tissue capsule. In some cases, the capsule is lacking, and they seem to infiltrate the neural tissue which, however, does not show histological features of a true neoplastic infiltration. Lipomas of the corpus callosum sometimes occupy a large part of this structure, which appears more or less malformed up to complete agenesis. Lipomas of the third ventricle may grow and cross the foramen of Monro. Spinal lipomas appear elongated in the direction of the cord to which they are tenaciously attached, so that their surgical removal is practically impossible.

### 21.7.3

#### Microscopic Appearance

Histologically, they show the classical structure of mature adipose tissue, organized into lobes and lobules, with connective fibrous tissue bands. In frozen sections, methods for staining adipose tissue constantly demonstrate lipid material, mostly triglycerides, in the cell cytoplasm. In some cases, smaller cells with a hyperchromatic nucleus and acidophilic granular cytoplasm, similar to embryonal adipose cells, are seen among the mature adipocytes [128]. When the number of such cells is high, the structure of the tumor is similar to that of the xanthomas. The fibrous connective tissue bundles, besides subdividing the parenchyma into lobes and lobules, at the periphery of the tumor orient themselves in parallel and form a capsule. When the connective tissue is particularly abundant, these tumors acquire features of fibrolipomas. The blood vessels are scarce and are mostly represented by small arterioles and venules, but in rare cases they may be very numerous and show an angiomatous appearance [3577]. Calcifications have frequently been described as roundish concretions both in the capsule and in the surrounding tissue [3781, 434, 3741]. The presence of mature bony structures has been reported in some cases [434].

### 21.7.4

#### Prognosis, Treatment

Lipomas are histologically and biologically benign tumors. Total removal leads to complete cure without recurrence, but the site and mode of growth frequently impede total excision. From the practical point of view, spinal lipomas have a greater importance because they more frequently give rise to clinical symptoms [3421].

## 21.8 Hamartomas, Ectopias, and Ectopic Tumors

### 21.8.1

#### Hamartoma of the Hypothalamus

By definition, hamartoma is a benign, nodular, tumor-like mass formed by a mixture of differentiated tissues normally present in the organ in which it is found, but in an abnormal location [27, 2786, 1955]. This lesion is rare in the CNS and is most frequently found near the hypothalamus.

Macroscopically, it appears as a mass with well-defined contours which projects from the floor of the third ventricle into the meninges. It is often connected by means of a peduncle to the tuber cinereum and to the mammillary bodies [2786, 1980], or it is free or has more points of attachment to the hypothalamus [138, 2458, 3162]. It is whitish, hard, and homogeneous in appearance.

Histologically, it is composed of neurons of different shapes and sizes (Fig. 21.29a,c). According to some, they do not resemble those of the hypothalamus [1384, 3807], but others believe they do [1964, 2690, 616]. Myelinated and nonmyelinated fibers [2439], a normal glial component, and sometimes gliosis are found among the neurons (Fig. 21.29b).

The hamartoma is mostly found in children and is associated with precocious puberty. This association has been explained either by the existence of anatomical connections with the hypothalamus [2786, 3709, 1955], by the presence of LH-RH [1581, 619] and of GDH-RH [616] in the neurons of the hamartoma itself, or by compression on the hypothalamus [53].

The efficacy of surgical treatment for the endocrine syndrome is controversial [1581, 2790], even if the development of microsurgery has allowed marked improvements in surgical results [1581, 1833].

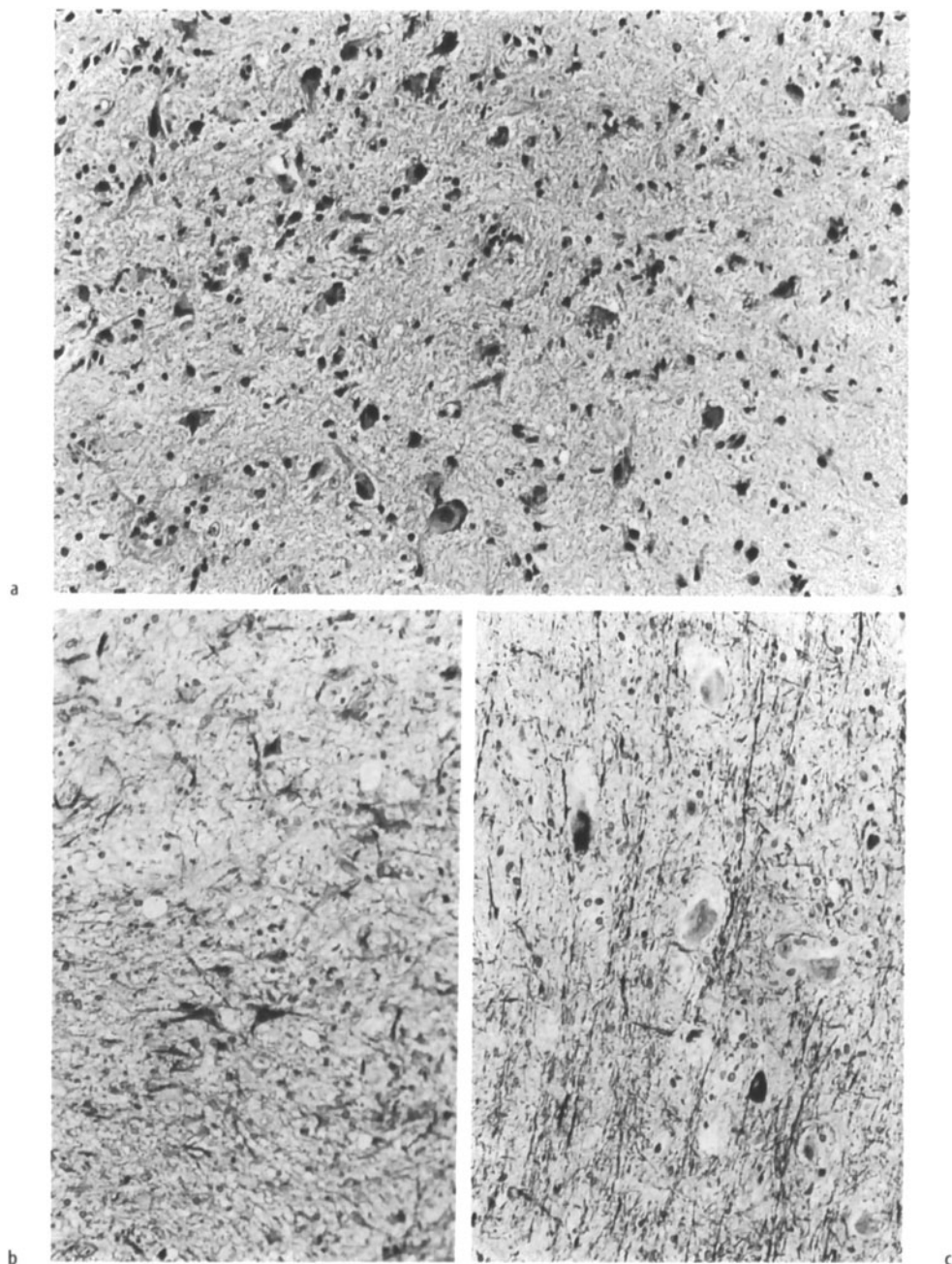
Hypothalamic hamartoma may be associated with multiple congenital anomalies: small or absent olfactory bulbs, absent hypophysis, hypoplastic adrenals and thyroid, cryptorchidism, cardiac and renal malformations, syndactyly, anal atresia, etc. (Hall-Pallister syndrome). It sometimes presents histological characteristics closer to a tumor so that its differentiation from a gangliocytoma or ganglioglioma becomes difficult.

### 21.8.2

#### Granule Cell Tumors

They have been described by Abrikosof [6], may occur in almost all organ systems, and are nodular in shape and mostly benign. Their cell origin has not yet been fully clarified: striated and smooth muscle cells, fibroblasts, Schwann cells, histiocytes, and mesenchymal cells have been considered as the cell source. Most probably they derive from Schwann cells [2342, 493, 2318].

A granular cell accumulation may be found in the posterior pituitary stalk and in the infundibulum as hamartomatous lesions, the so-called choristomas or tumorettes [3134, 403]. Sometimes they change into tumor.



**Fig. 21.29a–c.** Hamartoma of the hypothalamus. **a** Abnormal neurons and glial cells. H&E,  $\times 200$ . **b** Glial fibrillary acidic protein (GFAP)-positive reactive glial cells. PAP-DAB,  $\times 200$ . **c** Neurons positive and negative for neurofilaments (NF), SM31. PAP-DAB,  $\times 200$

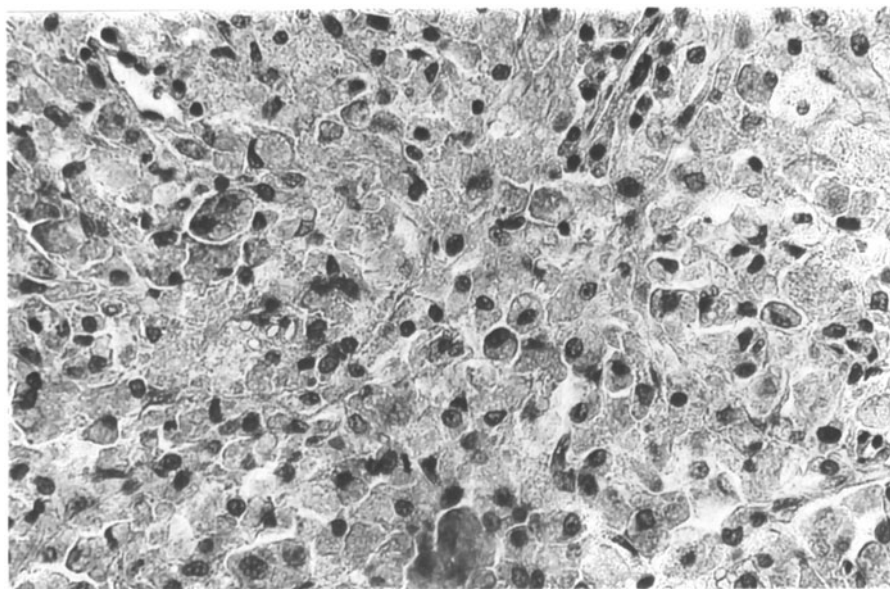


Fig. 21.30. Granule cell tumor. H&E,  $\times 200$

Very rarely, they occur intracranially, in the sella region [180, 3520], or intracerebrally [524]. They show mostly a malignant behavior, and histologically their nature seems to be astrocytic [3102, 1757, 727] or mesodermic and mesenchymal [2351, 1385].

The tumor has a high cell density and is composed of large and small cells, with a cytoplasm containing PAS-positive granules (Fig. 21.30), infiltrating the nervous tissue. The cells accumulate around vessels. Immunohistochemistry reveals contrasting results, showing positive staining for GFAP in some cases and for histiocytic markers in others. In the case studied by Claassen et al. [524], there was a positive staining for  $\alpha_1$ -antichymotrypsin and with MB2 antibody for B cells, and a negative staining for GFAP, indicating a “lymphoma-like” character. Immunoelectron microscopy demonstrated in a case a positive GFAP staining in some granular cells devoid of filaments, indicating the astrocytic origin of these cells [3549].

Even though the tumor is associated with a short survival, good responses are seen with radiotherapy.

### 21.8.3

#### Meningeal Gliomas

There is no doubt as to the existence of ectopic glial nests in the meninges, especially in children. They are usually found in the vicinity of the foramina of Luschka or in the sacrococcygeal segments of the spinal cord and more rarely on the convexity of the cerebral hemispheres. Gliomas may arise from these nests. Their identification is, however, difficult, because one must exclude exophytic growth of a hemispheric

astrocytoma. Rare cases in which the meningeal origin of the tumor was definite and others in which doubt could be present have been recorded [2904].

The same considerations are valid for the rare intradural extramedullary gliomas reported, while many doubts envelop the cases of primary meningeal gliomatosis.

#### 21.8.4

##### Ectopic Gliomas and Neural Hamartomas

Rare examples of hamartomas or masses resembling astrocytoma have been described at various sites: The orbit, pericranium, submandibular and sacral extraspinal regions. There are exceptional reports of intra-abdominal neuroepithelial tumors, for example, ependymomas of the ovary and of the broad ligament [1710, 189] and astrocytomas of the endometrium [3760, 2041, 1952].

The "nasal glioma" deserves particular mention. This term was introduced for the first time by Schmidt (1900) [3056] to indicate intra- and/or extranasal glial tumors. It is very rare, as only 55 cases had been described up to 1950 [264].

It has been hypothesized that this neoplasm could have the same origin as the encephalocele. It is known that in the 3- to 5-week-old embryo, the anterior neuropore is open and connected with the nasal area through a path of epithelial cells. The brain may herniate at this site, and thus when the skull closes, neuroectodermal tissue remains isolated outside it. The closure of the skull may be incomplete so that a glial duct remains connected with the frontal cortex. Not every author agrees with this interpretation, especially because only a few of the tumors have been shown to contain neurons. However, it has to be noted that neurons when present could have undergone regressive changes. A good demonstration of the encephalocele theory was given by Smith et al. [3231], who rejected the possibility that the tumor could originate from a teratoma or from heterotopias because of the existence of a connection between the tumor and the brain. They reviewed 88 cases from the literature and added five of their own. The tumor was present since birth in 38 of 48 cases. It was extranasal in 60%, intranasal in 30%, and intra- and extranasal in 10%.

Histologically, it is formed by fibrous and gemistocytic astrocytes and by a vascular connective stroma. Neurons may be present in some cases. Mitoses are not observed. The tumor has a capsule formed by astrocytic processes, fibroblasts, and connective tissue. The tumor is usually surgically removed with good results. The risk is that of meningitis, especially in cases with an intracranial connection.

In the past years, some tens of cases have been added.

#### 21.9

##### Hamartomas or Vascular Malformations

They are partly hamartomatous and partly hamartoblastomatous lesions, formed by mesenchymal structures and vascular elements. They can be observed in the encephalon and spinal cord, in the meninges, and more rarely in the bones of the skull or vertebrae. The first organic classification of these lesions was that of Virchow

[3555], which influenced subsequent research and nosography. Among the main classifications are those of Cushing and Bailey [628], Bergstrand [206], and Dandy [645].

Cushing and Bailey [628] were the first to separate by scientific criteria the cerebral vascular malformations of hamartomatous character from true blood vessel tumors. Telangectasias, venous and arteriovenous angiomas were distinguished from hemangioblastomas. The main distinction was that in malformations the neural tissue is present in the intervacular spaces, while in general it is absent in tumors, where instead it is replaced by collagen or reticular stroma. It should be furthermore remembered that vascular malformations show a frequent tendency to calcify [222, 2604], and angioblastomas rarely do.

The incidence of vascular malformations in autopsy material varies from 0.1% to 4% of all tumors [1522].

Recent technical advances in neuroanesthesia, neurosurgery, and diagnostic and interventional neuroradiology with preoperative embolization have made it possible to manage these lesions. However, they continue to be dangerous, causing damage in 0.17% of people below 40 years [473].

The old classification of McCormick [2190] included five varieties: (1) teleangectasia, (2) varix, (3) cavernous angioma, (4) arteriovenous malformations (AVM), and (5) venous angioma. A new classification contemplates the same varieties, subdividing them into three locations [473].

### 21.9.1

#### Clinical Features

Clinical features vary according to age. Whereas neonates and infants present with high output failure or hydrocephalus, in adolescents clinical features are more frequently associated with intraparenchymal or subarachnoidal hemorrhages. Later, typical clinical signs are partial epileptic seizures. Cavernous angiomas of the temporal lobe have been found in 11% of interventions for epilepsy [363, 91]. Repeated bleeding and steal phenomena are responsible for progressive deficits and, in older patients, of dementia. In the spinal cord, vascular malformations may assume the course of a progressive disease.

### 21.9.2

#### Capillary Teleangectasias

Very often, they are unexpected autopsy findings and may easily be overlooked because of their small size. They are found mostly in adults, preferentially in the pons, less frequently in the cortex and white matter, cerebral peduncles, and dentate nucleus. In some cases, they are multiple.

Macroscopically, they appear as pinkish punctated areas, sometimes similar to petechiae. Microscopically, they are formed by dilated capillaries with a saccular appearance. Their wall is thin, devoid of smooth muscle or elastica, with a tenuous collagen reinforcement. Normal neural tissue is present between the capillaries.



It is rare for capillary telangectasias to cause spontaneous hemorrhages. This eventuality is, however, fatal if the malformation is located in the brain stem. Under the heading of capillary telangectasia, Russell and Rubinstein [2904] put the “calcifying hemangioma” of the temporal lobe [2604], already considered as a telangectasia [3519].

### 21.9.3

#### Cavernous Angioma

This malformation often gives rise to neurological symptoms, both when it is located in the cerebral hemispheres and when in proximity to the ventricles and in the spinal cord, and may be a frequent cause of hemorrhage, especially in neonates. The incidence is very variable in different series: It has been calculated to be between 5% and 13% in autopsy series [3195]. Asymptomatic examples uncovered at autopsy also exist.

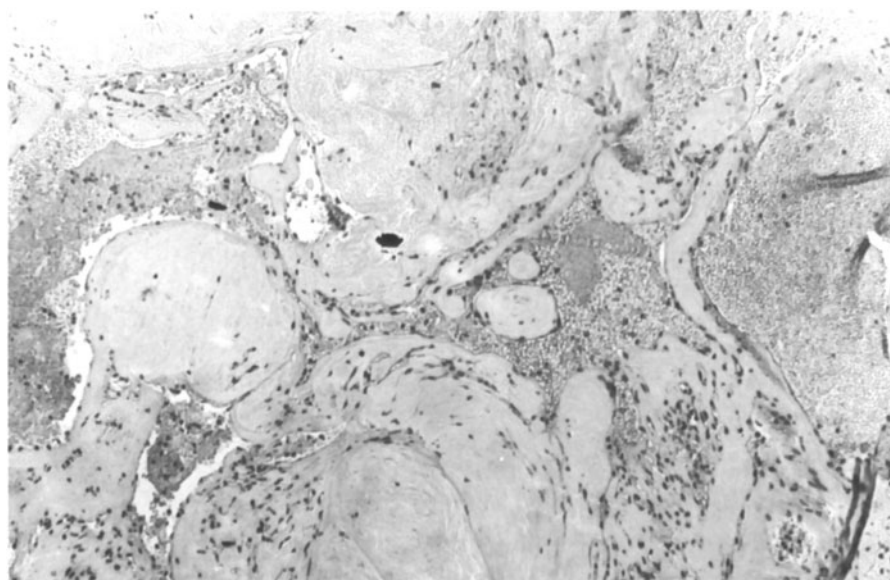
The age more frequently affected is the third to fourth decade, with an equal distribution among the sexes [3561]. The possibility of diagnosing the lesion precociously has recently been achieved with improved imaging quality, for example with MRI, and this has slightly modified the age incidence at diagnosis. After the 164 patients studied some years ago [3561], another 166, 41 of whom were under 18 years of age, have been reported [1313]. Seventeen patients between 18 months and 16 years of age and 19 between 7 months and 17 years of age [3109] have also been reported. The lesion is preferentially supratentorial, in particular affecting the rolandic fissure, the temporal lobe, and, less frequently, basal ganglia and the walls of the third ventricle. Below the tentorium, the preferred sites are the pons, less so the cerebellum, and rarely the spinal cord.

The lesion is usually single, sometimes multiple, and may also have a familial incidence [1075, 1275] or be associated with similar malformations in other organs. It is variable in size, even reaching conspicuous dimensions, and well circumscribed, has a lobulated appearance, and is dark red in color. On the cut surface, it may show cavities of various dimensions and sometimes calcifications. The surrounding neural tissue is yellowish.

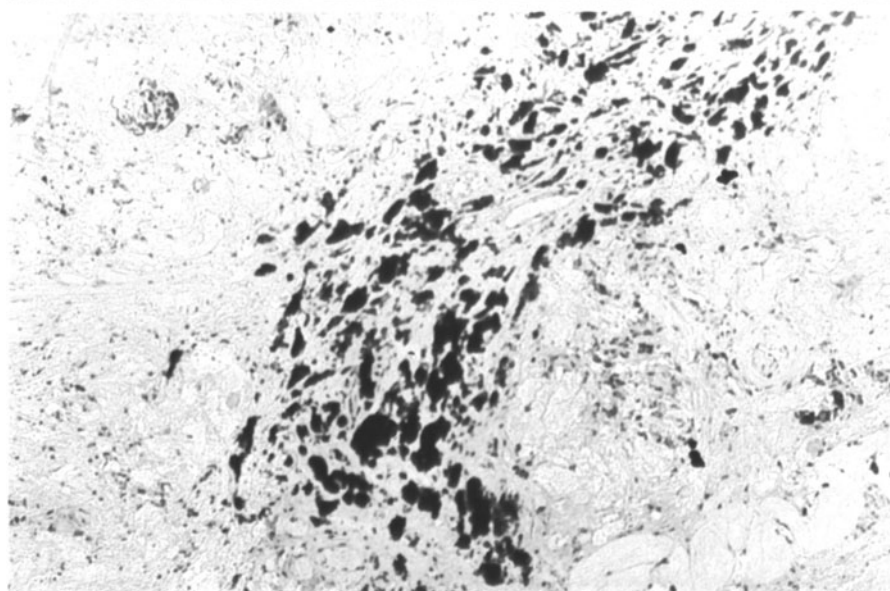
Microscopically, cavities of various sizes, lined by endothelium and with a collagenous wall which may even be very thickened, are seen (Fig. 21.31a). Elastic fibers may be seen [3195].

Old hemorrhages, hemosiderin pigmentation, and calcification with hyaline thickening of the vessel walls are frequently seen (Fig. 21.31b). The consequences of previous hemorrhages may be found between the cavities. There are thrombosis and organization phenomena with heavy reticulin production. In the tissue surrounding the lesion, there is no increase in blood vessels and, therefore, no supplementary blood supply. This is thought to be one of the reasons why the cavernous angioma may not be seen on angiography [3589].

Reactive gliosis is constantly present. With CT, the lesion appears as a well-demarcated area of hyperdensity. With MRI, it appears as one or more hyperintense spots in a hypointense halo (Fig. 21.32). The latter is due to accumulation of hemosiderin, which quenches the proton signal.



a



b

**Fig. 21.31a,b.** Cavernous angioma. **a** Aspect of the vessels. **b** Hemosiderin accumulation at the interface. H&E,  $\times 200$



Fig. 21.32. Cavernous angioma. Typical aspect on magnetic resonance imaging (MRI)

#### 21.9.4

##### Arteriovenous Malformation

The lesion is also known by the improper name of arteriovenous angioma or arteriovenous aneurysm: In fact, it is neither a tumor nor an aneurysm.

Its incidence varies between 0.5% and 1% of all tumors [3803]. It is already present in infancy and may cause hemorrhages, but it usually manifests itself in adulthood [1550]. There are observations in favor of a higher risk of spontaneous hemorrhages in AVM in infancy and for a high incidence of hemorrhages as a first symptom of cryptic AVM. Percentages and risk factors have been accurately calculated [1151, 3679]. Men are slightly more affected than women.

The preferred site of the AVM is often the territory of the middle cerebral artery, where the mass has its base on the meninges and its apex in the depth of the parenchyma. Other arteries may also be implicated. The venous drainage occurs through superficial and deep venous channels, for example, the system of the veins of Galen. At this point, the aneurysmatic dilatation of the central vein of Galen has to be remembered [3101, 1522].

The cerebellum is rarely implicated, but often it may be the site of cryptic AVM which are demonstrated after they hemorrhage. In the personal series, there are 13 cases of this type. The spinal cord is rarely involved. On the other hand, AVM may be found in the dura, especially in women over 40 years of age.

AVM may exceptionally be multiple [1522]; sometimes, instead, they are associated with single or multiple so-called berry aneurysms [3679], which involve the blood vessels supplying the AVM. It has not been established whether they are produced by the malformation itself or whether they are secondary to increased blood flow.

The AVM appears as a wormlike packet of blood vessels, which pulsate at operation, and is covered by a gray-bluish arachnoid. The underlying cerebral convolutions are atrophic and pigmented because of previous hemorrhages. Calcifications related to fibrotic and atheromatous phenomena may be present, usually in the older age group.

Some are called cryptic because they are not seen on angiography, but are really AVM of very small dimension; they are found, as has been said, mainly in the cerebellum [3589]. Microscopically, altered arterial and venous-type blood vessels are present. The former show a modification of the tunicae: duplication or interruption of the elastica, thickening or thinning of the muscle layer. The veins show collagenous thickenings. The arrangement may be modified by thrombosis, calcifications, and atheroma. In the adjacent neural tissue there are infiltrates of lymphocytes, macrophages, iron pigment, and gliosis.

Using angiography, the mass of tangled vessels may be seen with feeder vessels which may vary. One or more dilated veins go from the malformations to the dural sinuses. Sometimes the lesion may be missed by angiography and even by CT. MRI may be positive in these cases.

Surgery may be dangerous, especially for deep lesions, and many such lesions are considered inoperable. Alternative treatments include embolization, proton beam radiation, and  $\gamma$ -knife radiosurgery.

A total of 10% of patients die after the first hemorrhage and 10% after the second one. For subsequent hemorrhages, the risk is 20% [473]. A 25-year follow-up demonstrated that one fifth of patients were still neurologically intact.

#### 21.9.4.1

##### *Dural Arteriovenous Malformations*

Dural AVM represent a small percentage of AVM. The uncertainty concerning their frequency is due to the possibility that they are acquired lesions, mainly post-traumatic. Dural AVM invariably involve dural sinuses, and their arterial supply comes from the middle meningeal artery or its branches. The clinical symptomatology depends on the location and is usually due to subarachnoid or subdural hemorrhage.

Spinal dural AVM are quite common. Feeders are radiculo-medullary arteries. The venous drainage is accomplished through epidural veins or intraspinal coronal plexuses.

#### 21.9.5

##### *Venous Malformations*

These anomalies usually affect the spinal cord and occur in both sexes between 20 and 60 years of age [3729]. In the spinal cord they lie on the dorsal surface, between the high thoracic segments and the cauda equina (Fig. 21.33). In the brain they are mostly situated in the territory of the middle cerebral artery. A frontal location is the most frequent [1028].



Fig. 21.33. Venous angioma of the spinal cord

Macroscopically, the lesions appear as worm-like convolutions. On sectioning, the cord shows penetration by venous blood vessels, atrophy, and gliosis. Veins with walls thickened by collagen and hyaline material sometimes involve both leptomeninges and nerve roots. Softening and cyst formation may be found in the cord.

These lesions may be associated with cutaneous port-wine angiomas [1522].

Venous angioma was probably missed before CT and MRI were developed. By angiography, it appears as a system of small, converging veins ending in one large vein (caput Medusae) or in a meningeal vein. There may be some confusion with capillary teleangectasia

## Phakomatosis and Dysgenetic Syndromes

This is a group of pathological conditions characterized by malformations involving more than one system. The skin is frequently involved, and so these diseases have also been called the “neurocutaneous syndromes,” but this term does not encompass all possible pathological entities in this group; thus, the term “phakomatosis” is more widely used. This simply refers to the term phakoma (φακος=lens) which van der Hoeve [3503] gave to the small hyperplastic formations of the retina. These are genetically determined syndromes and, therefore, generally familial. In the CNS the manifestations include tumors, hamartomas, and various malformations.

### 22.1

#### Tuberous Sclerosis (Bourneville’s Disease)

This is often a familial disease with an autosomal dominant inheritance with variable penetrance. The gene was originally localized to the long arm of chromosome 9 [976]. In approximately 30% of affected families, the disease is linked to the gene on 9q. More than one gene can cause the disease; molecular genetic studies have implicated another gene on chromosome 16p [1584]. Loss of heterozygosity (LOH) for markers in the 16p candidate region supports the notion that the chromosome 16p gene functions as a tumor suppressor gene [1161].

However, the majority of cases arise sporadically. It should be remembered that incomplete forms are very frequent in relatives of patients so that the familial incidence is difficult to calculate.

Hence, as in other hereditary tumor syndromes, genotype does not strictly predict phenotype.

The associated CNS tumor is the already mentioned “giant cell subependymal astrocytoma” (see Chap. 9). Moreover, in the cerebral convolutions there are foci in which there is a disturbance of the cytoarchitecture with abnormal neurons and astrocytes, even of giant aspect. These are called tubers (Fig. 22.1) and give the disease its name; they are best demonstrated by magnetic resonance imaging (MRI). Characteristic of these cortical dysplasias is the presence of large cells with features of both glial and neuronal cells, without clearly being identifiable as one or the other [2783]. Subependymal astrocytic foci may still be found (Fig. 22.2), appearing as “candle gutterings” and consisting of the same cells that are seen in the cortical tubers. There is some propensity for growth of these nodules, which are then called subependymal giant cell astrocytomas. The growth potential of a subependymal nodule is not predictable and can be followed up by serial imaging studies [3176]. The finding of simi-

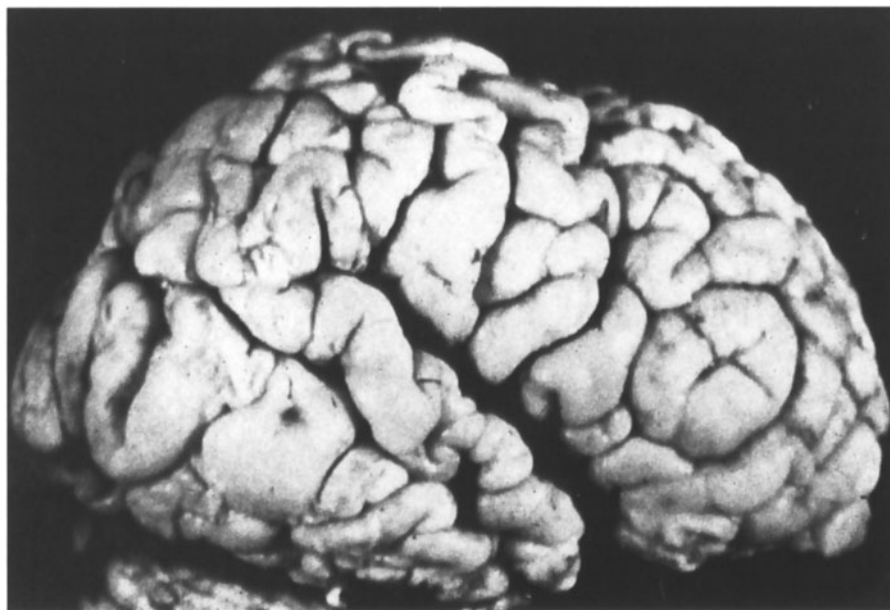


Fig. 22.1. Tuberous sclerosis, cortical tuber

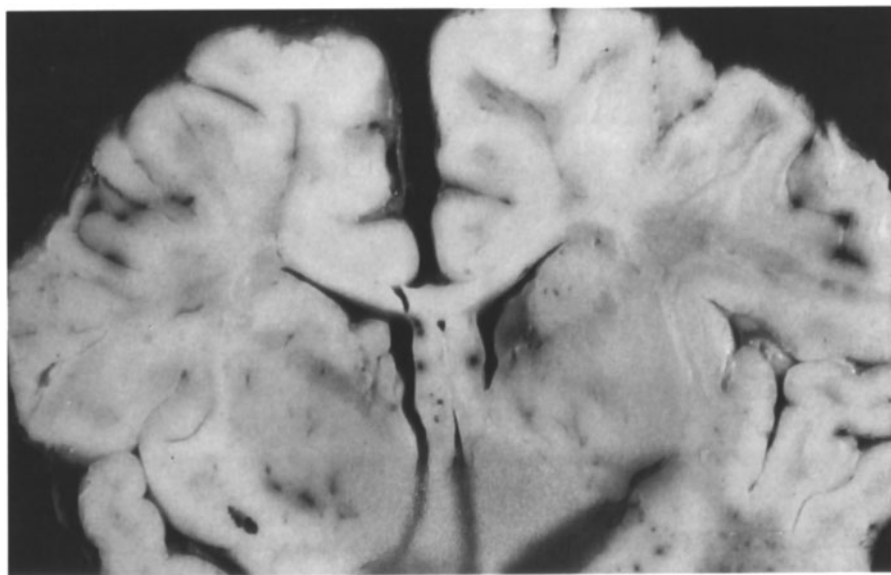


Fig. 22.2. Tuberous sclerosis, subependymal nodules

lar cell types in the different cerebral lesions of tuberous sclerosis supports the hypothesis that abnormal migration is inherent in the altered function of the putative genes [3178]. There are also rarer forms of cerebral tumors, with a variety of labels. In two children and a neonate, a hamartoma of the anterior olfactory lobe and in the olfactory germinal layer has been described. It was formed by whorls of giant glial cells and gliosis with further, sparse giant cells and small undifferentiated cells similar to the germinal cells. Cardiac tumors were also associated in these cases [674].

Full reviews on the topic are available [749, 1131, 3178].

Among the cutaneous changes, sebaceous adenomas (Pringle's adenomas) of the cheeks, depigmented patches, "café au lait" spots, raised and rough areas of skin (peau de chagrin), and angiofibromas of the nail grooves (phakomas of Koenen) have also been described. Retinal gliomas are characteristic (phakomas of van der Hoeve). Cardiac rhabdomyomas, liver adenomas and lipomas, adenomas of the pancreas and kidney, colonic carcinomas, and more frankly malformative lesions such as horseshoe kidney and micropolycystic degeneration of the lung are often seen.

From the clinical point of view, mental deficiency and epilepsy are the usual manifestations. It is possible to demonstrate the cortical tubers by means of MRI scanning [2442], confirmed by examining formalin-fixed brains with the same technique [2443].

## 22.2 Neurofibromatosis

Neurofibromatosis is a familial disorder inherited in an autosomal dominant manner, which manifests itself in two forms [2780, 2875, 1441], peripheral neurofibromatosis (NF1) and central neurofibromatosis (NF2). These differ greatly in frequency, the former having an incidence of 1/3000 and the latter of 1/37 000. Many cases are sporadic, and this disease has a high degree of spontaneous mutations [2904].

Genetic linkage studies in large families have shown that NF1 and NF2 have separate chromosomal loci (see Chap. 2). Concordant manifestations have been reported in homozygotic twins [24], and histologically identical malignant tumors have been observed in different members of the same family [3065].

Multiple neurofibromas are characteristic of the peripheral form. These may appear on peripheral and autonomic nerves or near nerve endings in the skin and viscera. When they involve the trunk of the nerve, they are of the plexiform type. Typical neurinomas may also be found, although these are mostly solitary (Fig. 22.3) and very often associated with neurofibromas.

A relatively frequent event is sarcomatous transformation of the neurofibromas, which has been calculated to occur in 4.6% of patients, corresponding to an incidence of 1/1000 [774]. It only occurs in adults and is probably related to the duration of the lesions and their number. Regardless of whether such transformation is [772] or is not [270] favored by irradiation, sarcomatous transformation is the main cause of death in the peripheral form of neurofibromatosis [2875]. NF1 also features cutaneous manifestations such as "café au lait" spots and lentigo in the axilla.

The central form [1026, 1587, 2136, 3649] is characterized by bilateral acoustic neurinomas, multiple neurinomas and neurofibromas of the cranial and spinal



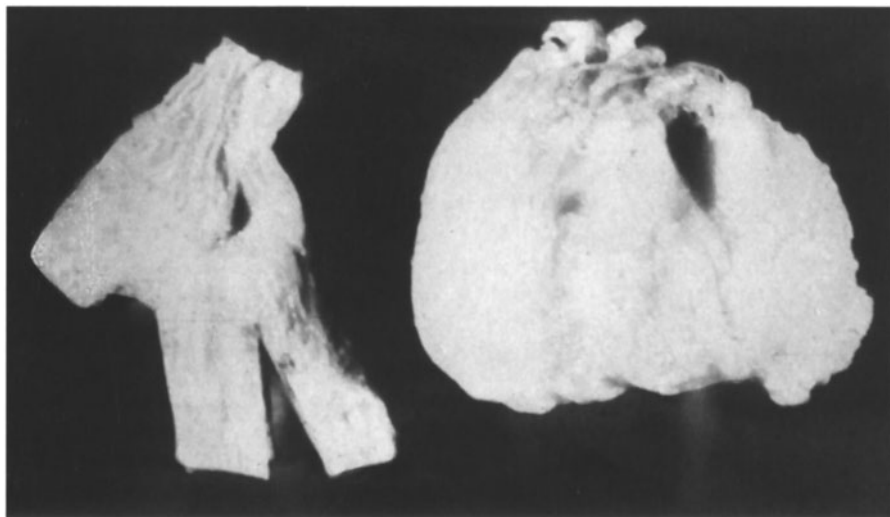


Fig. 22.3. Von Recklinghausen's disease, neurinoma of Gasser's ganglion (*right*) compared with normal ganglion (*left*)

nerves, and gliomas of the brain and spinal cord. The most frequently affected nerve is the eighth, while in the spinal canal sensory roots and the cauda equina are mostly affected. Bilateral acoustic neurinomas, however, are not necessarily associated with central neurofibromatosis [2904]. Intramedullary (see Chap. 17) and, exceptionally, intracerebral neurinomas have also been described [610].

Multiple meningiomas, usually of fibroblastic type, and gliomas, although rare, are part of NF2, and the latter may also be found in NF1. These are usually pilocytic optic nerve astrocytomas, presenting mainly in infancy. It has been calculated that a high percentage of optic nerve gliomas in infancy occur in the context of neurofibromatosis [310, 1457]. Pilocytic astrocytomas of the third ventricle may be found, sometimes with signs of anaplasia [1457, 2904]. Furthermore, cerebellar astrocytomas with signs of malignancy [1457], anaplastic astrocytomas at various sites, hemispheric astrocytomas, spinal astrocytomas, and spinal ependymomas are sometimes seen.

Other tumors may be part of von Recklinghausen's disease. Among these are pheochromocytoma, peripheral neuroblastoma, ganglioneuroma, paraganglioma, and carcinoid tumor of the duodenum. This range of tumors has caused many authors to consider neurofibromatosis as a generalized "neurocrestopathy."

Neurofibromatosis is the most common phakomatosis. It is a congenital disease characterized by dysplasias and/or tumors of tissues and organs derived from embryonic ectoderm, mesoderm, and endoderm; patients present mainly with cutaneous and nervous system lesions. There are two types, NF1 and NF2, the first of which is the more frequent and is also called von Recklinghausen's disease.

### 22.2.1

#### Neurofibromatosis-1 or von Recklinghausen's Disease

NF1 is an hereditary disease transmitted in an autosomal dominant fashion with an incidence of 1/3000. Fifty percent of patients do not show a positive family history, suggesting a high mutation rate in the NF1 gene. NF1 gene consists of over 350 kb of genomic DNA and contains 59 introns [1950]. The protein product, called neurofibromin, contains 2818 amino acids. It is present in the adult nervous system in high quantities and is distributed in cell bodies and dendrites of large neurons which project the axons long distances. In Purkinje cells, it is localized in the endoplasmic reticulum. It can be found in oligodendrocytes, but not in astrocytes, endothelial cells, or microglia cells [2451]. Neurofibromin is detectable both in affected patients and in normal subjects. In affected people it may be nonfunctional. The NF1 gene has 100% penetrance, but a highly variable expressivity.

A wide variety of lesions may be present in NF1 patients, but the diagnosis is based on some particular lesions, as the NIH consensus conference has established [2429]. There are the following: "café au lait" spots, which must be over 5 mm in pre-puberal and 15 mm in adult people; two or more neurofibromas or one plexiform neurofibroma; axillary frecklings; optic glioma; two or more Lisch nodules, i.e., pigmented hamartomas of the iris; osseous lesions. Café au lait spots appear in newborns, and there must be more than six of them. Neurofibromas may be multiple and appear in three forms: (1) dermal neurofibromas, which are nonencapsulated, circumscribed lesions, mainly composed of spindle-shaped cells and collagen fibers, located in proximity of peripheral nerves or trunks; (2) plexiform neurofibromas affecting nerve trunks and malignant forms, generally called malignant peripheral nerve system tumors (MPNST; see Chap. 17); and (3) diffuse neurofibroma. Other tumours may be present, such as pheochromocytoma, carcinoid tumors, rhabdomyosarcoma, either alone or as part of Triton tumors, astrocytoma, and leukemia. Other features may also be present, such as macrocephaly, intellectual handicap, epilepsy, headache, aqueduct stenosis, hydrocephalus, and hypertension [3571]. In three cases of NF1, an intense astrocytic gliosis has been found, both in the cortex and in the white matter. The gliosis may be secondary to neuronal damage or may be primarily determined [2451].

An observation of primary importance is the occurrence on MRI of unidentified brightening objects (UBO) in the brain of children with NF1, associated with so-called specific learning disability. It is very difficult to ascertain the pathologic nature of these findings, especially as they may disappear with time [1476]. In three cases, UBO localized in the internal capsule, globus pallidus, and white matter corresponded at autopsy to vacuolar or spongiotic changes; the accumulated fluid was responsible for the high signal intensity on T2-weighted images [723].

The gene has been found in 17q 9–11 [150, 3120] (see chap. 2).

### 22.2.1.1

#### *Clinical Course*

Benign schwannomas of the brachial plexus are uncommon tumors. They are benign and can be easily excised. Cases of multiple concurrent and recurrent benign schwannoma have been reported, probably representing a new subtype of neurofibromatosis [1472]. Complications of the disease are numerous and may be fatal. They increase with age, and death occurs almost exclusively in adults, rarely in children [1763].

### 22.2.2

#### **Neurofibromatosis-2**

NF2 is also known as central neurofibromatosis. It has an incidence of 1/37 000 and is inherited in an autosomal dominant manner with high penetrance. Half the patients have no family history and represent new mutations. The diagnostic criteria include the following [1442, 3177]: (1) bilateral vestibular schwannomas, (2) a first-degree relative with NF2 and affected by a vestibular schwannoma or two of the following: meningioma, schwannoma, glioma, neurofibroma, lens opacity, brain calcification, or (3) two of the following: vestibular schwannoma, multiple meningioma, or schwannoma, glioma, neurofibroma, lens opacity, brain calcification.

Schwannomas do not differ from sporadic tumors in terms of location and the nerve involved, but they do differ as far as multiplicity and earlier age of onset are concerned. Cutaneous schwannomas affect half the patients. Histologically, they differ from sporadic tumors in that they have a more lobulated aspect [3243] and a multifocal appearance along the same nerve. They show higher labeling indices (LI) for MIB-1 and proliferating cell nuclear antigen (PCNA) than sporadic cases [74]. Malignant transformation is very rare [2022], but is possible [3672].

The term schwannosis refers to a proliferation of Schwann cells in the spinal dorsal root entry zones, associated with schwannomas of the roots or the perivascular space in the spinal cord [2904]. It may also occur as a reactive response to local injuries, but may be seen as a reaction to ependymomas, meningiomatosis, and meningoangiomatosis independently of NF2.

Cutaneous neurofibromas, like schwannomas, may be multiple, and in NF2 there is no plexiform neurofibroma [2779]. Multiple meningiomas are typical. They occur earlier in life than sporadic tumors and are always benign. The observation that they are mostly of the fibroblastic type has not been confirmed [2022]. Meningoangiomatosis is a rare condition characterized by meningeal plaques over the cortex with a proliferation around small vessels of meningotheial or fibroblastic cells. It has been described either as sporadic or in association with NF2. It was previously considered to be part of von Recklinghausen's disease, but this was erroneous. It is usually associated with bilateral acoustic schwannomas [2022].

Neuroepithelial tumors are less common than schwannomas and meningiomas. Most of them are intramedullary or cauda equina tumors, rarely of the medulla, and are represented mainly by ependymomas [2904]. It must be noted that ependymal heterotopias have been seen in NF2. Diffuse and pilocytic astrocytomas are less com-

mon than ependymomas. Glial microhamartomas can be found in the cerebral cortex, as clusters of cells, with large nuclei and eosinophilic, stellar cytoplasm; these are considered to be astrocytes [3672]. They can also be found in basal ganglia and cerebellum, thalamus, and in dorsal horns of the spinal cord. Both in the cortex and in the spinal cord, they must be considered together with ependymal heterotopias [2904].

### 22.2.3

#### Associated Lesions of a Dysplastic Nature

There is a variety of lesions of a dysplastic nature seen in neurofibromatosis which are often microscopic and may be associated with tumors or have a tendency to grow like tumors. Their pathogenesis is difficult to identify but is almost certainly related to what was once called “dysgenesis.” This in turn recalls the *Gliadysgenesien mit blastomatösem Einschlag* of Bielschowsky [234], not specific for von Recklinghausen’s disease but found in other forms of phakomatosis such as tuberous sclerosis.

Dysplasia associated with central neurofibromatosis involves the Schwann cells, glial cells, and meningeal cells. In the first instance, there is intramedullary schwannosis, situated in the posterior horns and characterized by Schwann cell foci and reticular fibrils, in continuity with neurinomas of the root. Perivascular schwannosis in the spinal cord is seen in relation to ependymomas, meningiomatosis, and meningoangiomatosis, which may be seen outside the context of neurofibromatosis. Abnormal nests of glial cells may be found associated with the dysplasia mentioned above. Nests of ectopic ependymal cells may be seen associated with ependymomas, syringomyelia and calcification [2904]. These nests of glial cells have an evident cytoplasm and pleomorphic nuclei of astrocytic nature and sometimes contain blepharoplasts [2904].

Dysplastic lesions in the cerebral cortex and the basal ganglia have been fully described in six cases [3672]. They have pleomorphic and multinucleated glial cells with blastomatous features but no mitotic activity. They are immunohistochemically negative except for S-100 protein and have been defined as “glial microhamartomas.”

Among the various dysplastic lesions associated with NF1 are the “subependymal glial fibrillary nodules,” represented by small protuberances in the ventricular wall and containing a proliferation of fibrillary glia. They recall the *feinfaserige Gliose* of granular ependymitis [1496] and can cause aqueductal stenosis [2896]. Already described in NF2 [2867], they have since been described in NF1 after examination of a large series [1399]. Apart from the lesion described above, there are other forms of gliosis, found in various locations and sometimes not easily distinguished from astrocytoma; also, micronodules of proliferating blood vessels in the cerebral parenchyma have been found [2904].

### 22.3

#### Von Hippel-Lindau Syndrome

In von Hippel-Lindau (VHL) syndrome, there is an association between cystic cerebellar hemangioblastoma [1966], retinal angiomas, or von Hippel’s disease and

congenital cysts of the pancreas, kidney, liver, and lung, with renal and adrenal, solitary or multiple tumors.

Benign cysts, vascular tumors, and carcinomas occur; affected tissues often have multiple lesions. Not all the classical lesions are present in affected families, and affected members of a family may have only a single lesion. Minimal diagnostic criteria modified from those classically proposed [2233] should consist of retinal angioma or CNS hemangioblastoma in a patient who has an immediate family member affected by at least one typical lesion of VHL syndrome [2405, 2408].

The disease is inherited as an autosomal dominant trait with a high penetrance; the responsible genetic locus maps to the short arm of chromosome 3 [3122, 1879]. New mutations are presumed in affected cases without a family history. Different types of germline mutations have been detected in affected families, i.e., large deletions, missense mutations, microdeletion/insertions, nonsense mutations, and have a striking correlation with the classical type (occurrence of typical lesions) [487]. It is now possible to identify asymptomatic carriers of VHL [1094]. Mutation detection may be useful in the diagnosis in patients without a family history or in patients with a family history and without any other manifestation of VHL. The VHL gene is a tumor suppressor gene for specific cell types in the retina, CNS, adrenal gland, kidney, pancreas, and epididymis.

The incidence of hemangioblastoma in VHL family series ranges from 20% to 72% [2407]. The most common site is the cerebellum [1443, 295, 2344] followed by brain stem and spinal cord [356]. Most patients present with a CNS hemangioblastoma as a sporadic case [1777]; extensive clinical screening showed that 25% had VHL [931, 238]. Molecular genetic analysis may be of practical help in the diagnosis. Younger age at onset and multifocal lesions suggest VHL [2728]. Posterior fossa hemangioblastoma is an important cause of morbidity and mortality in VHL. Multifocal tumor development and recurrence remain a serious problem in the clinical management of these patients. In the pathogenesis of cerebellar and spinal hemangioblastoma, mutational inactivation of both copies of VHL gene are required [1586]. It is not known whether one or both cell types of the tumor (stromal cells and vascular endothelial cells) have gene inactivation.

## 22.4

### Sturge-Weber Syndrome

Also called encephalotrigeminal angiomatosis [588] or meningo-facial angiomatosis [3706], Sturge-Weber syndrome is characterized by a hemispheric capillary-venous malformation, with radiologically visible calcification, and a cutaneous nevus or a homolateral port wine nevus in the trigeminal region. Contralateral hemiparesis and partial motor seizures are often present. Homolateral buphthalmus and glaucoma may coexist, and mental handicap may be present as well.

Macroscopically, the lesion appears as a mass of small blood vessels in the leptomeninges and cortex, with foci of calcification.

Microscopically, it features large quantities of capillaries and veins situated in the pia and cortex, with hyaline degeneration of their walls. Calcification develops as fine granules in the capillaries, and calcospherites of various dimensions are formed by

confluence. Calcification involves the external layers of the cortex, sparing the pia. There is a reactive gliosis and neuronal loss.

The supposedly incomplete forms have been much discussed, while various associations with ganglionic ectopia, hemangiomas, and tumors have been reported.

## 22.5 Other Dysgenetic Syndromes

The Wyburn–Mason syndrome [3728], a sporadic disease, has many affinities with Sturge–Weber syndrome. It consists of an arteriovenous mesencephalic malformation associated with a cutaneous vascular nevus in the trigeminal territory and retinal angiomas.

Hereditary hemorrhagic teleangiectasia (Rendu–Osler–Weber disease) is autosomally dominantly inherited and may involve the CNS, with multiple blood vessel malformations of the teleangiectatic type [2821].

There are also “multiple angiomas” and the familial retinal cavernous angiomas.

Lastly, there is ataxia teleangiectasia or Louis–Bar syndrome, an autosomal recessive disease which affects children. This is characterized by progressive cerebellar ataxia, conjunctival and facial teleangiectasia, immune deficiencies with immunoglobulin anomalies (especially of IgA), hypersensitivity to the effects of irradiation, and a tendency to develop lymphoid tumors or other malignancies. The main neuropathological lesions are cerebellar atrophy due to maturation defects in the Purkinje and granule cells [1038, 3553], degeneration of the posterior columns of the spinal cord, and nucleocytoplasmic abnormalities of the satellite cells in the ganglia and in Schwann cells. Numerous other lesions, of both vascular and cellular type, have been described.

## Primary Central Nervous System Lymphomas

Primary lymphomas of the CNS (PCNSL) are tumors whose nosography has only been worked out in relatively recent times, but not all the problems have been resolved.

In the past, they were labeled with different names such as microgliomatosis, reticulum cell, perivascular, periadvential, adventitial, perithelial or reticuloendothelial sarcomas, malignant lymphomas, malignant reticuloendotheliosis, reticulohistiocytic encephalitis, granulomatous encephalitis and lymphoproliferative diseases. At the base of the old conception was the so-called reticulum cell, which is an undifferentiated element capable of evolving toward both macrophage and lymphocyte lines and, in the CNS, into microglia.

The resemblance of these tumors to the extraneural lymphomas had already been commented upon in 1943 by Kinney and Adams [1684].

The reticulum cell is not normally positive to silver carbonate staining [2126]. It becomes positive only after macrophage differentiation and, in the CNS, after microglia differentiation. Microglia cells were considered the cells of origin of the tumors [3766, 193]. However, as these tumors show both positive and negative cells, they were separated into reticulum cell sarcomas (negative) and microgliomas (positive).

A series of objections to this concept were raised. First of all, argyrophilia could not be considered a basis for separating the two entities, given the similarity of the histological aspects and of their clinical features [402]. Furthermore, argyrophilia is not enough to establish the microgliomatous nature of the cell. Lastly, the perivascular arrangement of tumor cells suggest that the tumor may originate from the perivascular histiocytes of the brain, rather than from microglia which lie free in the nervous tissue. It was, therefore, proposed to unify these tumors under the term "reticuloendothelial cell sarcoma," which emphasized the histiocytic nature and left aside the relationship with microglia [402].

The abundance of "lymphocytes" admixed with tumor cells had been stressed [402]. Only later [1294] was a clearly lymphocytic variant identified in this group of tumors, with two subclasses: pure lymphocytic and lymphoplasmacytoid, depending on the presence of lymphocytes or immature (lymphoplasmacytoid) plasma cells, on the basis of Rappaport's classification of extraneural lymphomas [2352]. The lymphocytic variant was the most frequent in the group, the histiocytic variant (reticuloendothelial cell sarcoma) being much less common. Furthermore, argyrophilic cells were few compared with the exuberant proliferation of lymphoid cells and undistinguishable from reactive microglia, without any transitional forms. On this basis, the cell of origin of these tumors (from now on called lymphomas like their extracerebral counterpart), was considered to be an undifferentiated mesenchymal cell,

capable of lymphoid and stromal differentiation, ubiquitously distributed and favoring the adventitial space.

From 1960 on, malignant lymphomas were reclassified according to immunologically based schemes [2042, 1916, 757, 3284]. The tumors were supposed to be the product of altered hematopoiesis, associated with a defect in the mechanisms of regulation, maturation, and/or differentiation of cells of the immune system. The majority of lymphomas are formed by a predominant cell population, analogous to a cell type of the normal pathway of differentiation. Therefore, they are classifiable according to the properties of lymphocytes expressed during normal development and differentiation. The demonstration of intracytoplasmic immunoglobulins and membrane antigens, employing methods commonly used to characterize B and T lymphocytes, led to the discovery that the majority of the so-called extracerebral "reticulum cell sarcomas" have features of B cells and, hence, have been classified as B cell lymphomas [3297]. A similar study of cerebral reticulosarcomas demonstrated that these tumors are B cell lymphomas of immunocytic, immunoblastic, and lymphoblastic type, containing intracytoplasmic immunoglobulins. The argyrophilia seen in cerebral tumors is similar to that of extracerebral lymphomas and indicates the reactive histiocytic component associated with lymphomas [1417]. It does not depend on the tumor location but on the occurrence of cells producing immunoglobulins, which are thought to stimulate a histiocytic reaction and the production of reticulin fibers [1915]. The term "microglioma" has, therefore, been abandoned. These tumors are today considered fully fledged lymphomas. A meta-analysis confirmed that the majority of PCNSL are B-cell neoplasms with intermediate to high-grade histology [1531]. In 1994, a revised European American Lymphoma (REAL) classification was created, based on available morphologic, immunologic, and genetic information and not strictly based the theoretical pathway of lymphoid differentiation [1245].

Primary cerebral lymphomas must be distinguished from a secondary involvement of the CNS by systemic lymphomas. Primary cerebral lymphomas are intraparenchymal tumors and may either present as a single or, frequently, as multicentric foci. They affect subjects who do not have systemic disease. For a long time, the tumor remains localized to the encephalon. The estimated incidence of systemic spread of PCNSL ranges from 3% to 27% [1358, 402, 1294, 1530, 1286, 2001, 217]. A careful review of the literature suggests that occurrence is in fact rare; systemic relapse develops 3–35 months after diagnosis and is not necessarily associated with CNS relapse [355]. It is difficult to state whether late systemic lymphoma represents distant relapse of the cerebral tumor or progression of covert systemic disease. Secondary lymphomatous involvement of the CNS is generally a neoplastic infiltration of the subarachnoid (lymphomatous leptomeningitis) or the subdural or epidural spaces, which may lead to compression of the spinal cord. Cerebral involvement is clinically manifested in 5%–10% of patients with a systemic lymphoma [1937] and in 20%–30% at autopsy [1526]. However, lymphomatous intraparenchymal deposits have also been described during the course of systemic disease [1524, 1937]. A median survival of 1 year has been noted with primary cerebral tumors and of 2 months only, for cerebral involvements by extracerebral lymphoma [2062].

Ocular involvement has been frequently reported in association with cerebral lymphomas [687]. It may be either a direct extension of the brain lymphoma or another site of a multifocal disease.



### 23.1

#### Frequency, Age, Site, and Clinical Features

Primary cerebral lymphomas represent 0.3%–1.5% of all intracranial tumors and 0.9%–2% of all malignant lymphomas [957, 1294, 1530, 217, 3717, 1541, 3025]. In the personal series they represent 2.2% of all intracranial tumors. There is an increased incidence in immunosuppressed patients, after renal [497, 2605] and cardiac [230] transplantation, in systemic lupus erythematosus [1978], during Epstein-Barr virus (EBV) infection [2573, 1360], and in the Wiskott-Aldrich syndrome [1284] and other hereditary [973] or acquired [3242] immunodeficiency syndromes. A dysfunction of T suppressor lymphocytes with a consequent proliferation of a clone of B lymphocytes is thought to occur.

An increased incidence has been reported since the beginning of the century [2416, 756], but it cannot be adequately explained by the increased frequency of immunodepressive syndromes [1358] and seems to be unrelated both to acquired immunodeficiency syndrome (AIDS) and organ transplantation.

Two cases of lymphoma associated with meningioma have been reported [3223]. Radiation-induced PCNSL have occasionally been reported [3299]. Cerebral lymphomas occur at all ages (from 16 months to 90 years), with a peak between the fourth and sixth decade.

The incidence is 1.5–2.5 times greater in men than in women [297].

The frontal lobe is most frequently involved (up to 36% of cases) followed by temporal lobe, parietal lobe, deep nuclei, occipital lobe, cerebellum, and brain stem [2362, 3449]. Positive cerebrospinal fluid (CSF) cytology at initial presentation is found in 10% of cases; the CSF protein is usually markedly elevated. CSF cytology alone without cerebral computed tomography (CT) scan changes rarely leads to the initial diagnosis of PCNSL [1844]. Spinal cord lymphomas are very unusual [3218]. A primary meningeal localization has only rarely been described [2125, 141].

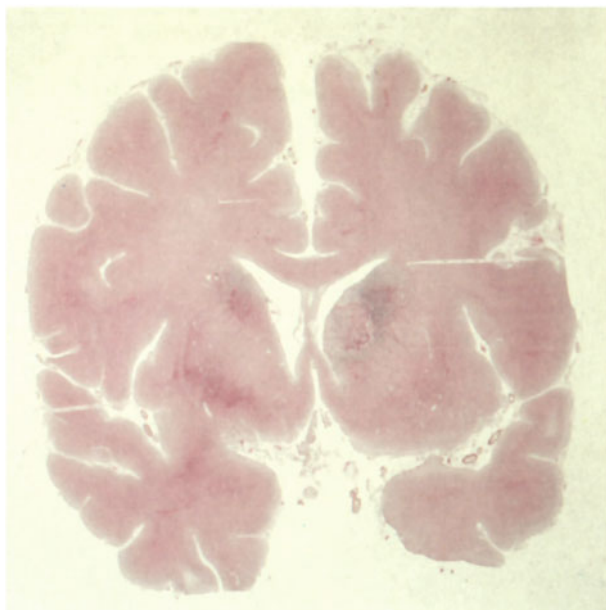
There are no specific clinical signs. Symptomatology largely depends on the location. When the tumor is strictly localized, the clinical presentation is monofocal. When the lesions are multiple, there is a clinical polyfocality.

The presentation is generally characterized by focal neurologic deficits, neuropsychiatric symptoms, seizures, and signs of increased intracranial pressure, in decreasing frequency. Symptoms are usually present for a short duration, with a range of 1 week to 24 months (median, 8 weeks) [3449]. Many cases have been published with different initial symptoms.

### 23.2

#### Macroscopic Aspect and Imaging

The recognition of primary lymphomas is difficult, because they may be confused with other processes. In immunodeficient patients, the differential diagnosis with toxoplasmosis may be difficult when the lesion shows an enhancing ring on CT. Diagnostic difficulties, however, also exist when the lesion has a typical appearance; for example, a solitary hyperdense mass can be confused with a meningioma. When the lesions are multiple, other multifocal processes are to be differentiated.



**Fig. 23.1.** Lymphoma affecting basal ganglia and temporal lobe

Angiography has little role. The use of positron emission tomography (PET) is still under study.

Primary cerebral lymphomas present as single or multiple lesions (Fig. 23.1) which occur in 22%–45% of cases [1294, 1286, 3717, 2247]. Sometimes they appear as a diffuse and symmetrical infiltration of the basal ganglia, brain stem, and ventricular walls, with involvement of the corpus callosum and “butterfly” growth in the white matter of the hemispheres.

At neuroimaging the occurrence of multiple lesions is frequent (up to 45% of cases). The appearance on CT is distinctive; the tumor is hyperdense or isodense, as a homogeneously enhancing mass with indistinct margins (Fig. 23.2). Lesions are frequently periventricular and surrounded by a mild to moderate edema. With magnetic resonance imaging (MRI), the lesions are usually hypointense to isointense on T1-weighted images and isointense to hyperintense on T2-weighted images [2822]; they may have a higher signal intensity following gadolinium injection [3790]. CT and MRI scanning are sensitive indicators of the response to treatment and may detect relapse before symptoms reappear.

### 23.3 Microscopic Appearance

The tumor is composed of roundish cells, with a mosaic-like pattern and a preferentially perivascular distribution. The nuclei have different, categorized forms, and the number of mitoses is variable (Fig. 23.3). The tumor is more widespread than it appears macroscopically. At a distance from the tumor center, foci of proliferation may

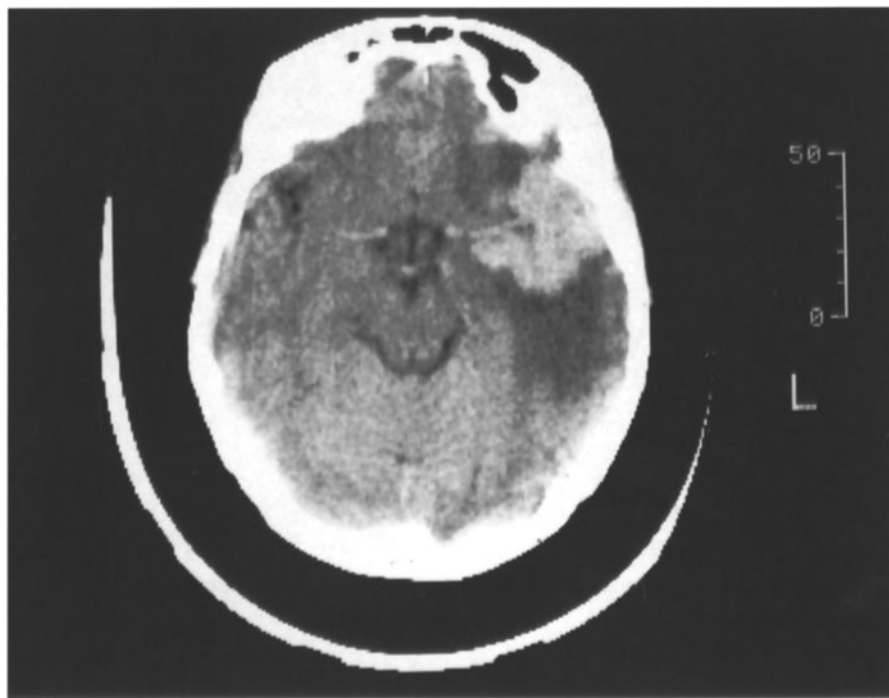
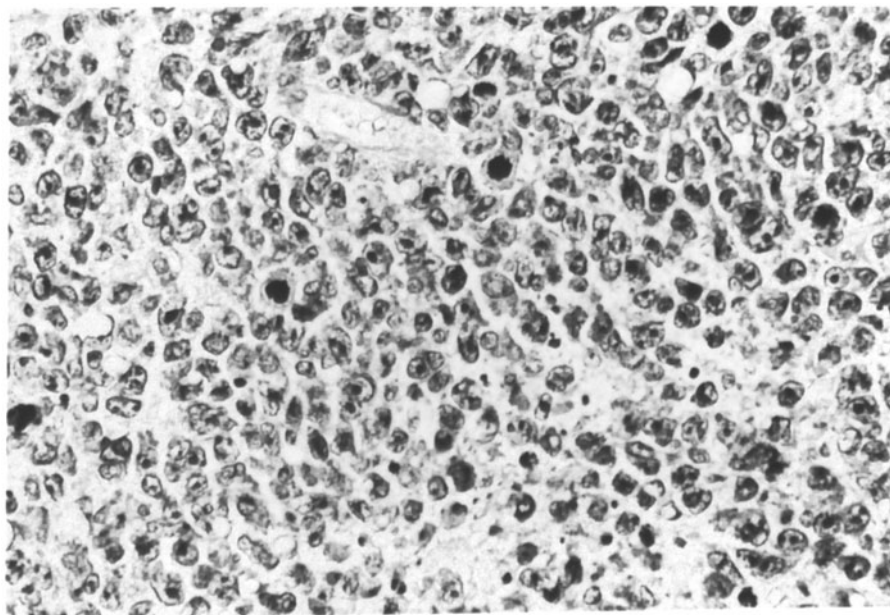


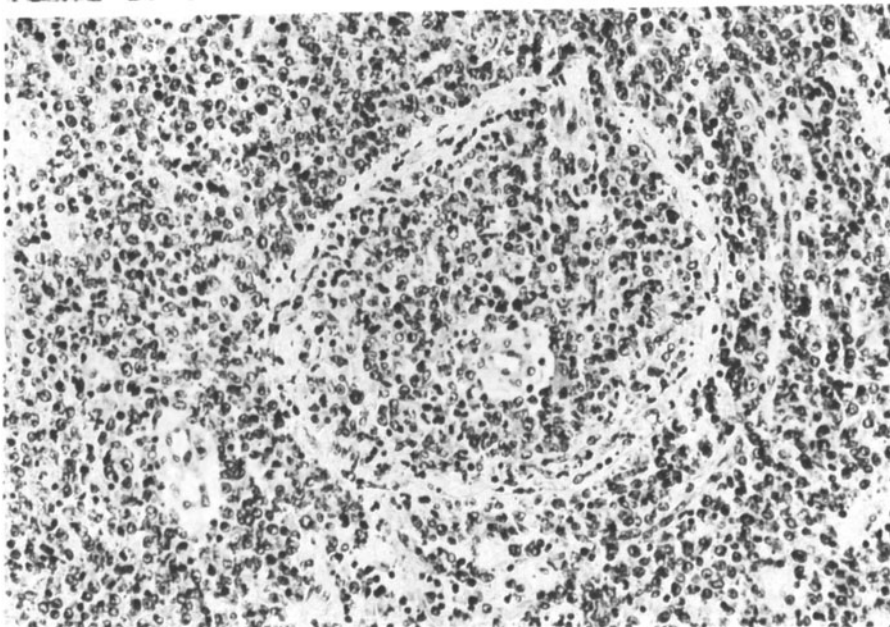
Fig. 23.2. Lymphoma on computed tomography (CT) scan

be found, characterized at their periphery by cell proliferation in the perivascular spaces (Fig. 23.4a,b). Sometimes, the latter are accompanied by an inflammatory picture, simulating encephalitis, with perivascular sleeves, composed of small mature-looking lymphocytes and rare plasma cells (Fig. 23.5a). They have been considered to be part of an immune cellular reaction against the tumor, as in other cerebral tumors [1646]. However, the monoclonality of the plasma cells [1417] and the abundance of these perivascular sleeves suggest that they can be preneoplastic lymphatic stages.

The perivascular arrangement of the tumor cells, evident also in the main tumor, is a characteristic feature. The rims of the perivascular cells are separated by concentric rings of reticulin (Fig. 23.4c,d), corresponding to basement membrane containing laminin (Fig. 23.6) [1079], collagen types III, IV, and V, and fibronectin [1573, 1733]. In the intervacular areas, reticulin is much less abundant, even though it appears in relation to the perivascular network (Fig. 23.5b). It is not produced by tumor cells, as originally thought when they were considered as cells of the “reticulum,” but it derives from the thickening and fragmentation of the basement membranes consequent to the growth of tumor cells in the perivascular space [1079]. Cells of a histiocytic nature and containing fibronectin have been seen both around the blood vessels and in the tumor. They could have a role in reticulin deposition, as hypothesized in extracerebral lymphomas [1915]. An alternative hypothesis is that cerebral pericytes or astrocytes may produce reticulin in an attempt to arrest the diffusion of foreign cells [1573].

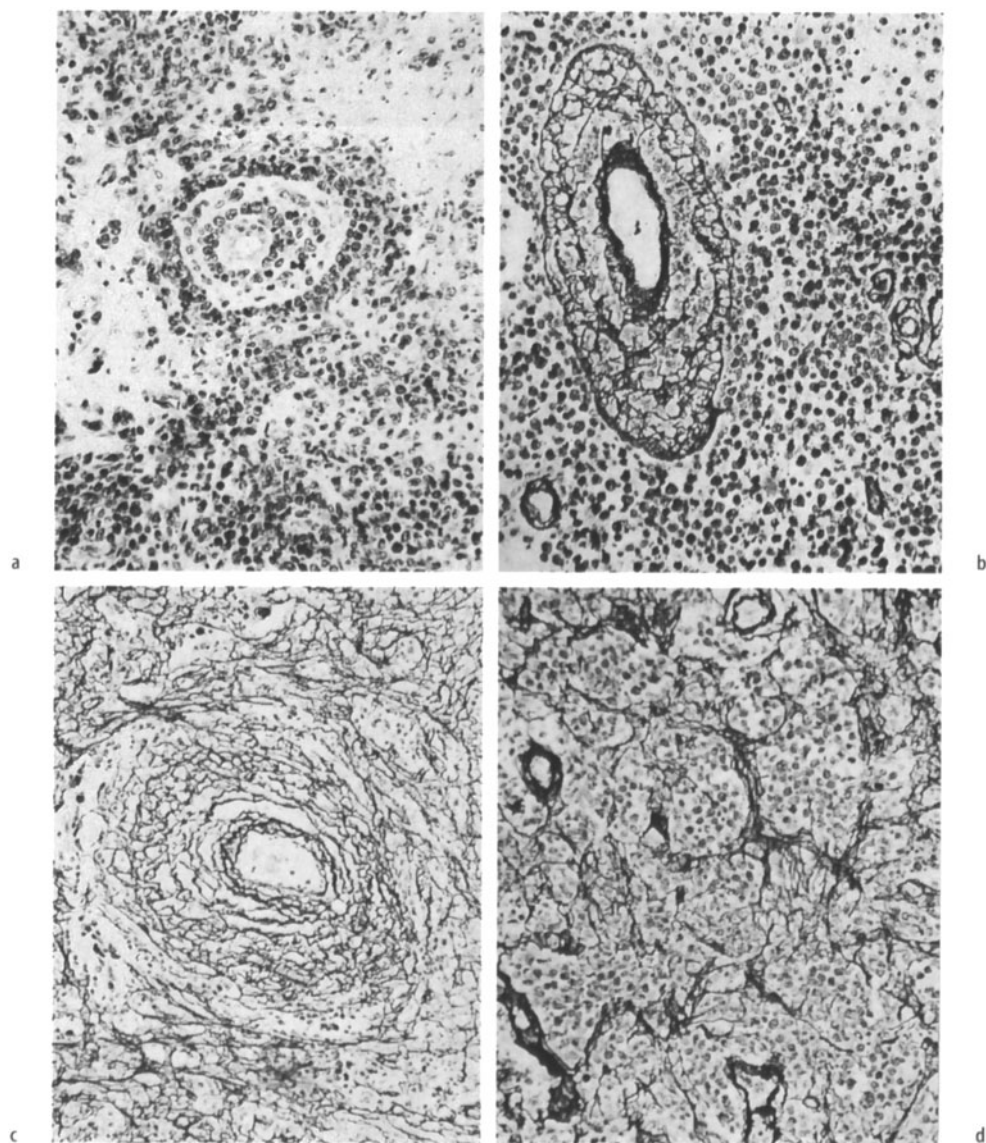


a



b

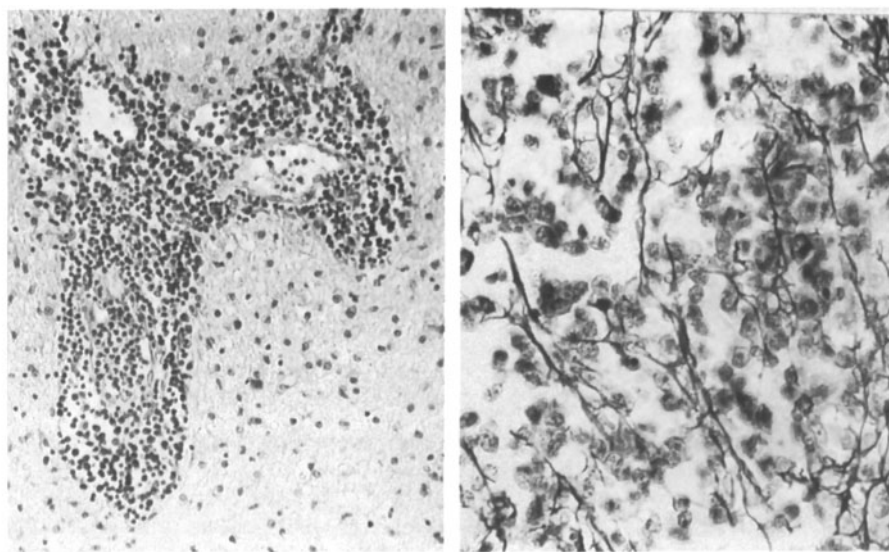
**Fig. 23.3a,b.** Brain lymphoma. **a** Typical aspect with frequent mitoses. H&E, ×400. **b** Perivascular growth of the tumor. H&E, ×200



**Fig. 23.4a–d.** Brain lymphoma. **a** Perivascular sleeve of tumor cell. H&E,  $\times 300$ . **b** Idem, with concentric reticulin rings. Gomori,  $\times 300$ . **c,d** Perivascular rings of reticulin in the tumor. Gomori,  $\times 200$ . (From [2994])

Cerebral lymphoma, therefore, originates in the perivascular spaces, to which it initially remains confined and from which it subsequently infiltrates and destroys the cerebral parenchyma.

Monoclonal and polyclonal cytoplasmic immunoglobulins have been demonstrated by immunohistochemical techniques applied to paraffin sections in a propor-



**Fig. 23.5a,b.** Brain lymphoma. **a** Perivascular sleeve of lymphocytes and plasma cells. H&E,  $\times 200$ . **b** Distribution of reticulin fibers among tumor cells. Gomori,  $\times 300$ . (From [2994])

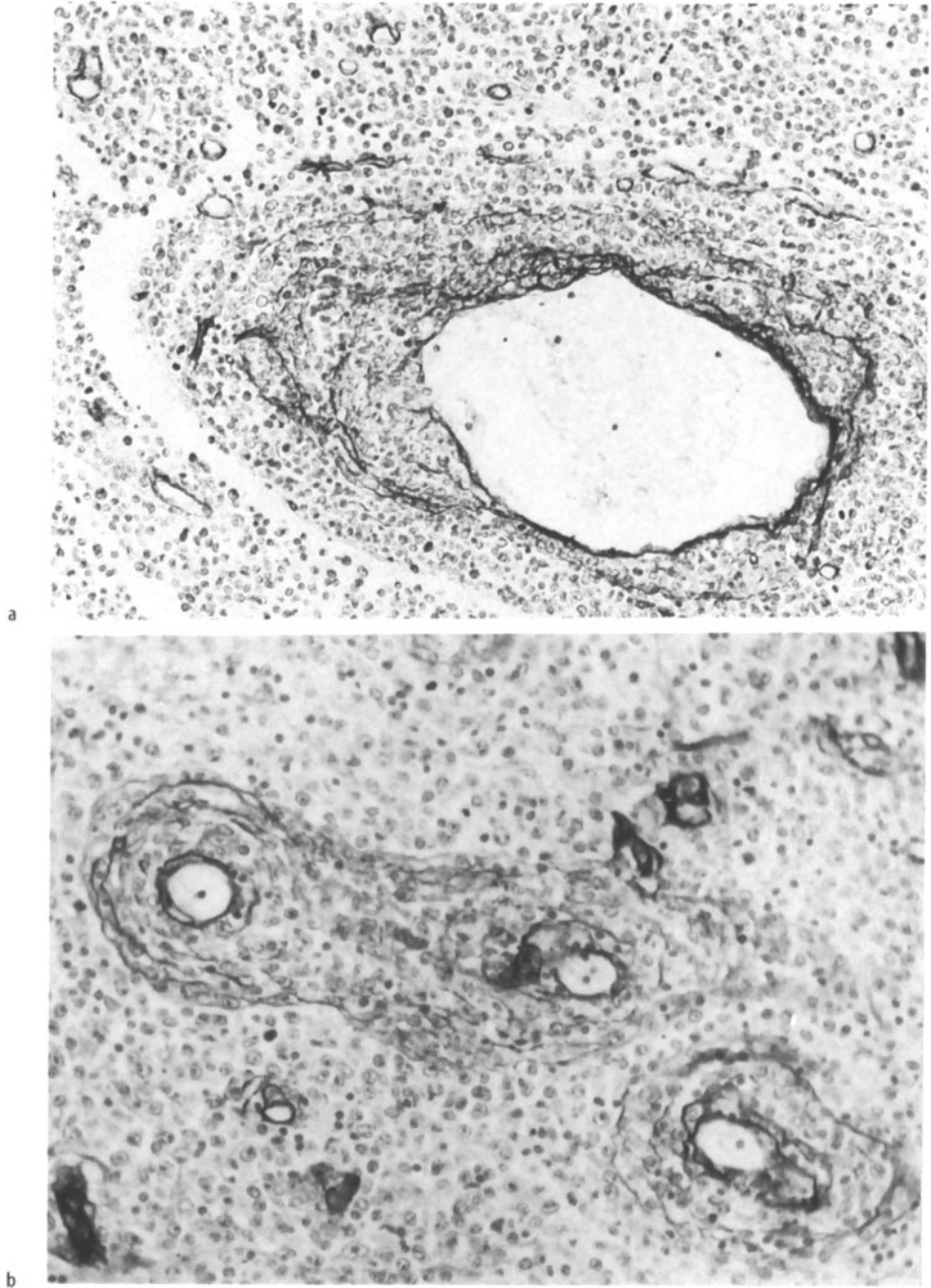
tion of cases [1417, 3404, 1924, 39, 2247, 3199, 756]. This is in agreement with a B cell origin of these tumors, confirmed by the expression of other B cell surface [1807, 1032, 168] and intracytoplasmic [3025, 756] antigens. In general, cerebral lymphomas express B cell differentiation [9] antigens corresponding to a more mature phenotype than extracranial lymphomas [1032]. A rearrangement of the immunoglobulin genes has also been demonstrated in four cases, which confirms the nature of the B cell lymphomas [1808].

Antigens of the T lymphocyte series (UCHL1, OKT-11, and Leu 1) have been demonstrated either in sparse cells and in cells of probable reactive nature [1807, 3025, 872] or in the majority of the cell population in a tumor, considered as a T lymphoblastic lymphoma [3025].

Other T cell lymphomas have been reported [2125, 288, 2315].

Cells bearing histiocytic markers (lysozyme,  $\alpha_1$ -antitrypsin,  $\alpha_1$ -antichymotripsin) that are present in some cases have been considered to be reactive histiocytes [2247, 756, 3199], as in extracerebral lymphomas [599]. There are also cells of reactive microglia (Fig. 23.7).

Further confirmation of the lymphomatous nature of the tumor cells does not help with the problem of the origin of the tumor cells in primary cerebral lymphomas, the brain being an organ devoid of lymphoid tissue. The development of cerebral lymphomas in the perivascular space is in agreement with the hypothesis of their origin from a mesenchymal pluripotent perivascular cell [1294]. Hematopoietic pluripotent stem cells have, in fact, been demonstrated in the brain of adult rats [164]. An origin from lymphocytes of the choroid plexuses and arachnoid membrane has also been suggested [3163]. The antigenic resemblance of glia to normal and tumor lymphocytes [3666] and the cross-reactivity of lymphoma cells with specific glial anti-



**Fig. 23.6a,b.** Brain lymphoma, perivascular rings of laminin. PAP-DAB,  $\times 200$



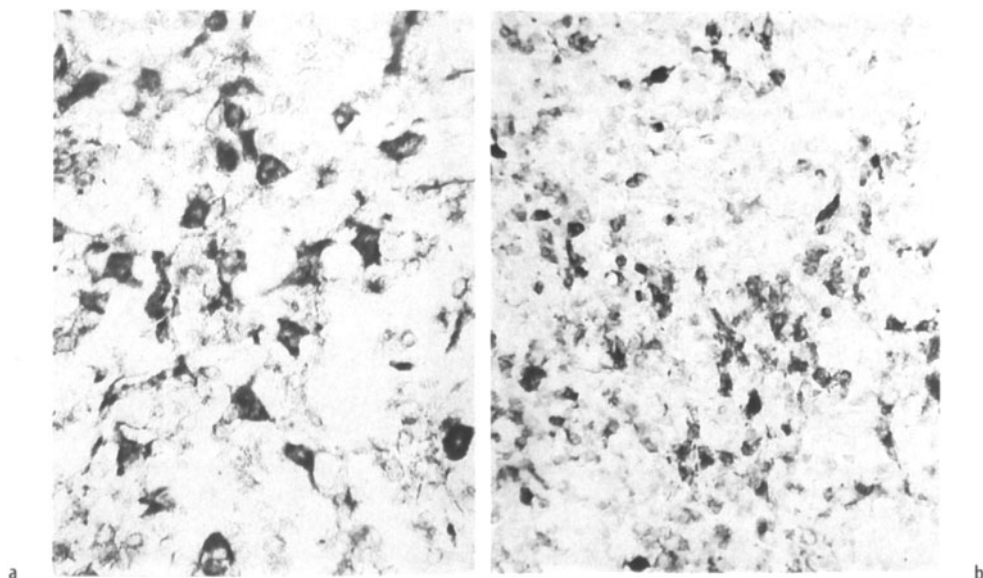


Fig. 23.7a,b. Reactive microglia cells. **a** Hortege silver carbonate,  $\times 400$ . **b**  $\alpha$ -naphthylesterase,  $\times 300$

gens seem to suggest that glia also have a role in the pathogenesis of cerebral lymphomas [288]. However, the perivascular multicentric origin is also compatible with an origin of tumor cells from the blood.

Two theories as to the origin of cerebral lymphomas have been proposed, both supported by clinical and pathological findings [1358]. Reactive lymphocytes are attracted to the brain by an infective process, probably viral, and a second local event then transforms a reactive population into a neoplastic clone, with a superficial molecule specifically binding to the neural tissue and its endothelium. This could explain the high frequency of cerebral lymphoma in patients with AIDS, undergoing chronic immune stimulation due to repeated infections [3199]. Alternatively, the neoplastic transformation of B lymphocytes could occur in a lymph node or in an extranodal lymphatic site.

The neoplastic clone is supposed to reach the encephalon through the blood stream and settle only there, because it bears surface molecules specifically binding to the neural tissue. Both these hypotheses could explain the cerebral “primary onset,” and the second theory would account for the extracerebral localization of a cerebral lymphoma in 10% of cases. The existence of molecules specifically binding to an organ or tissue, called “homing molecules,” have been demonstrated on the surface of lymphocytes circulating in the lymph nodes [1012] and in subclones of malignant melanoma [2424]. Direct evidence for cerebral lymphomas does not exist at present, although it is known that some surface antigens are shared by hematopoietic and neural cells, in particular, HLA-DR [1265] and Leu-7/HNK-1 antigens [2613].

Indirect evidence of “lymphocyte homing” in brain tissue is the observation that the distribution of tumor subtypes seen in PCNSL is not the same as in systemic lymphomas; a selection of tumor types occurs with lymphocyte homing and passage



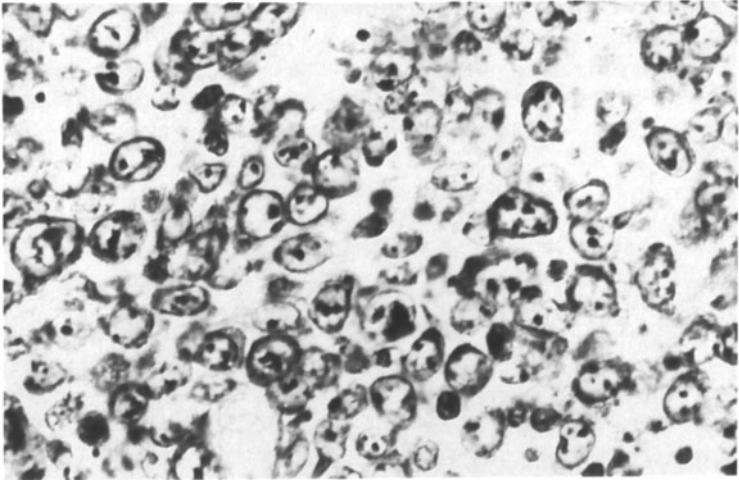
across the blood-brain barrier (BBB) [1531]. The identity of the selective homing molecules is as yet unclear; no difference has been found between PCNSL and systemic lymphomas as regards integrin expression [2576]. The crossing of the BBB by normal or transformed lymphocytes is critical to the formation of PCNSL; a localized perturbation of the barrier by injury or infection may be a prerequisite of lymphocyte migration [2314]. In immunocompromised individuals, PCNSL has a constant association with EBV, whereas in immunocompetent subjects, EBV has been detected in only about 17% of analyzed tumors [2063, 108, 169, 1197, 2586]. The precise mechanism relating virus to tumor pathogenesis is still unclear [2314]. Another suitable pathogenetic virus, human herpesvirus-6 (HHV-6), was found to be expressed in only one PCNSL out of 42 examined cases [2586].

If the distribution of various types of lymphoma is compared in the published series, evident discrepancies are noted, especially when the classification of Lukes and Collins [2042] is followed. The prevalence of immunoblastoma [1530, 3404, 1511, 676, 2247], lymphoplasmacytoid lymphoma [1417, 39, 3199], centrocyclic-centroblastic [756], centroblastic [3266, 3025], lymphoblastic [1257], and highly malignant unclassifiable lymphoma [288] has been reported. Authors who have followed Rappaport's classification agree on the prevalence of the histiocytic diffuse type [3404, 1924, 1286, 3717, 958]. According to the International Working Formulation system [757], the predominant histological classes are immunoblastic (Fig. 23.8a), small noncleaved (Fig. 23.8b), and large noncleaved lymphoma [1286] or large immunoblastic lymphoma [1358], that is high-grade malignancy tumors. Also low grade tumors, for example, plasmocytoma (Fig. 23.8c), are included.

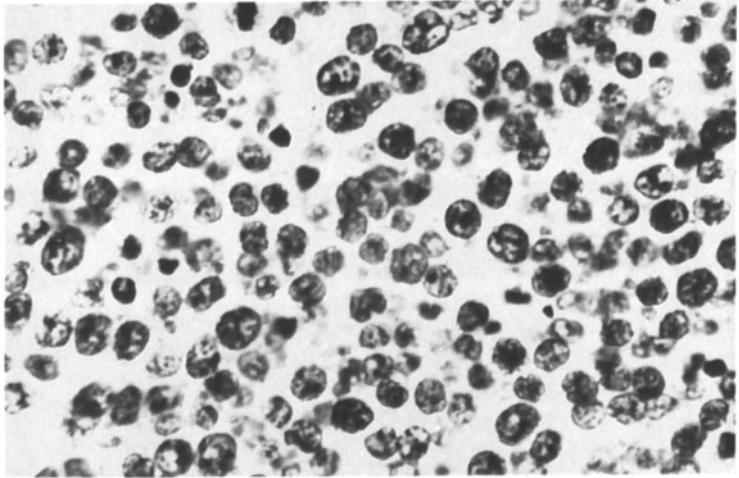
These discrepancies derive from the uncertainties of the classification of lymphomas and from the great variability of aspects within the cerebral lymphomas. This variability depends on the evolution of the process: The morphologically predominant cell type changes from the appearance of a follicular center or lymphoplasmacytoid cell to that of a cell closer to the immunoblast [3404]. This fits in with the concept of the progression of noncerebral lymphomas from a follicular center cell lymphoma or lymphoplasmacytoid lymphoma to an immunoblastic sarcoma [2042]. While in extraneural lymphomas, the majority of cells are in the same phase of maturation, the opposite is the case in cerebral lymphomas. The presence in the latter of follicular center elements, reported in almost all series, may be explained only by this hypothesis of progressive maturation.

The unexplained discrepancy between the Working Formulation (largely American) series and the Kiel (largely European) series of PCNSL would not be solved up by reclassifying PCNSL with the REAL classification; the relevance of systemic classification systems to PCNSL has thus been questioned [2314]. Moreover, in PCNSL the prognostic value of histological subtypes is unclear, because nonuniform correlations between histology and survival times have been reported [1268, 1286, 2267]. Analysis of molecular abnormalities of systemic lymphomas has increased our understanding of lymphoma pathogenesis and made it possible to determine lesional clonality and molecular classification. During normal lymphocyte maturation, rearrangements in B cell immunoglobulin and T cell receptor genes take place and gener-

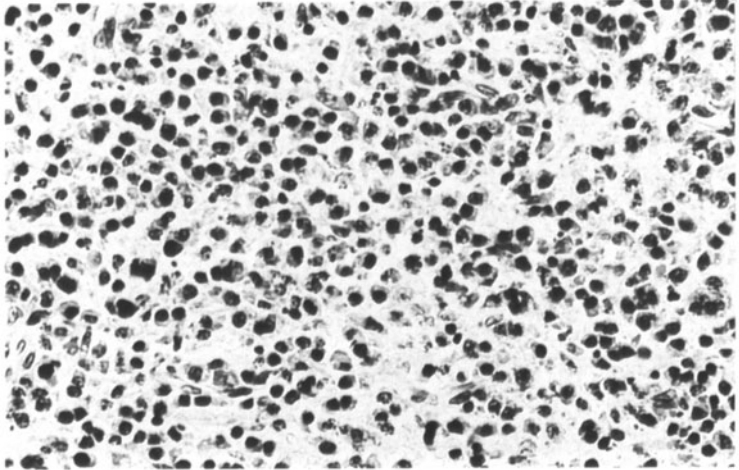
**Fig. 23.8.** **a** Immunoblastic lymphoma. H&E,  $\times 400$ . **b** Small, noncleaved cell lymphoma. H&E,  $\times 400$ . **c** Plasmocytoma. H&E,  $\times 200$  ▷



a



b



c

ate immunologic diversity. Abnormalities may arise at any point of gene rearrangement; if the erroneous event (translocation) involves a cellular oncogene, a lymphoid neoplasm arises. Characteristic translocations have been detected in B cell lymphomas [1168, 1719, 2474]. Little is known about which translocations are present in PCNSL [2226, 3063]. *Bcl-2* rearrangements are missing in PCNSL [1532].

## 23.4

### Epidural Lymphomas

Epidural spinal primary lymphomas have to be considered. They present at a site which is typical of systemic lymphoma, but they are mostly isolated, both at the onset and during their course [371, 1208, 1154]. Histologically, they are well or poorly differentiated, small cell, lymphocytic lymphomas and have a good prognosis, because of the low degree of malignancy and their radiosensitivity. These lymphomas originate either from preexisting lymphoid tissue in the epidural space, by diffusion in the paravertebral space, or via the blood in the peridural adipose tissue [1299].

## 23.5

### Lymphomas in AIDS

Primary cerebral lymphomas are common in AIDS patients [718]. In some series, they rank second after toxoplasmosis as a cause of focal neurological lesions, representing 5% of neurological complications [3239, 1941]. Except for the age of onset, which is obviously the same as that of the AIDS population, they do not differ in clinical characteristics from other primary cerebral lymphomas; in most cases they are multicentric [3242]. Pathologically however, they have unusual features, and it is difficult to subclassify them as to type, due to the very marked pleomorphism and small “noncleaved” cells coexisting with large immunoblasts [3242].

The constant association of EBV and PCNSL in immunocompromised patients with AIDS or organ transplantation suggests a possible viral origin of PCNSL. The expression of tumor suppressor proteins RB and p53 is upregulated following EBV infection [3360]. Immunocompromised patients have a supranormal number of EBV-infected lymphocytes [3339, 1387]; however, it has not been demonstrated that increased viral burden is quantitatively related to PCNSL.

The prognosis is clearly worse, survival being less than 2 months [3239, 1072]. It improves after radiotherapy (median, 2–5 months), although it remains shorter than that of non-AIDS patients [175, 1125, 2107]; selected patients may have a longer survival time (11–16 months) when treated with additional chemotherapy [474].

## 23.6

### Prognosis, Treatment

Some authors have reported a lack of correlation between the histological type and prognosis [1530, 676, 1615, 1268, 2267] but others found a longer survival to be related to certain histological types, such as the plasmacytoid lymphoma and centrocytic-

centroblastic lymphoma [288], the low-grade lymphomas according to the classification of Kiel [1511], and the “small cleaved cell” lymphoma [1358]. Overall, however, the prognosis is worse than in systemic nodal or extranodal lymphomas of the corresponding type. The prognosis is, however, better than for secondary cerebral lymphomas.

Surgical intervention is mandatory, also because in the majority of cases the diagnosis is only reached by histological examination. However, surgical procedures do not influence the prognosis. Survival after surgery alone is about 1 month, independent of the type of surgery [2362]. By stereotactic biopsy, an accurate histologic diagnosis is obtained [3161].

After a histological diagnosis of cerebral lymphoma, an appropriate “staging” investigation is required in order to exclude systemic non-Hodgkin lymphoma, even though the concurrence of cerebral and systemic lymphoma is infrequent [1358, 355].

The use of corticosteroids is advantageous per se and may cause a reduction in the tumor mass, with prolonged survival [3206, 3633, 3521]. Corticosteroids induce cell lysis, and consequently cerebral biopsy may be nondiagnostic [3521]; steroid responsiveness should not be used as a diagnostic test for PCNSL.

Postoperative radiotherapy gives good results as primary cerebral lymphomas are highly radiosensitive, although the control of the disease obtained by radiotherapy is transient and not comparable with that of extracerebral lymphomas. Postoperative radiotherapy produces lengthening of the median survival from 4 to 15 months [217, 1133, 2917, 1615, 2362, 3748], with a median survival of 55% at 1 year and 32% at 2 years.

There is no direct demonstration of a relationship between the radiation dose and survival [1133]. Doses of 35–45 Gy have been demonstrated to be efficacious [2917], but generally 50–55 Gy are given. Doses above 50 Gy have been effective [2362]. Whole brain irradiation and local radiation do not seem to affect survival differentially [1133, 2658], even if theoretical considerations seem to advise whole brain irradiation, for example, the tumor’s diffuse spread, its frequent multicentricity, and its recurrence in areas distant from the original tumor [958].

Chemotherapy for these tumors was given after it was noted that some patients responded very favorably, even though transiently, to corticosteroids [10]. These may be lympholytic, apart from reducing the edema [3685, 3206, 3521]. Not many patients have undergone chemotherapy alone or in association with radiotherapy. The drugs used include methotrexate, cytosine arabinoside C, BCNU, ACNU, CCNU, CHOP (cyclophosphamide + doxorubicin + vincristine + prednisone), BCOP (BCNU + cyclophosphamide + vincristine + prednisone), VENP (vincristine + cyclophosphamide + procarbazine + prednisone), dacarbazine, and procarbazine [1985, 1301, 3, 1924, 2236, 943, 288, 2362, 690]. There is no randomized study indicating the best protocol [961].

Methotrexate has been administered intraarterially with prior alteration of the BBB through intravenous and/or intrathecal osmotic agents [2414, 2417]. Modest improvements in survival have been obtained in various series. The global evaluation of treated cases gives a median survival of 13 months with 68% of patients surviving at 1 year and 27% at 2 years [1004]. The best results have been obtained with high-dose methotrexate therapy [1301, 2649, 846, 1004]. Overall, patients treated with methotrexate have a median survival of 19 months, 100% surviving at 1 year and 40% at 2 years [1004]. The results of chemotherapy have been inferior to those obtained in extracerebral lymphomas up to the present. The therapeutic problem is today considered in view of a different treatment for AIDS and non-AIDS patients.

## Metastases

### 24.1

#### Frequency

The exact figure of the frequency of cerebral metastases is unknown since the data from epidemiological, clinical, and autopsy series are inconsistent. In epidemiological studies, the average incidence varies from 2.8 to 11.1/100 000 and could be very close to that of primitive CNS tumors [3593]. That derived from clinical, neurological, and neurosurgical series increases from 3.5%–4.2% in the period 1930–1950, to 10%–13% in the 1960s [2994]. Autopsy series have yielded a figure of 15%–20% [2674, 3376].

Autopsy series give percentage values on average higher than those of clinical series, mainly because asymptomatic lesions are found. In the large series from the Memorial Sloan-Kettering Cancer Center of New York relating to the period 1970–1976 [2672], intracranial metastases were present in 24% of patients who died because of tumor. Nine percent of these were intracerebral only, without any involvement of the meninges. It has been estimated that from 20% to 50% of bearers of a malignant neoplasm develop cerebral metastases, which are the cause of death in 50% of cases [2782].

Tumors of the lung, breast, skin (melanomas), kidney, digestive tract, and choriocarcinoma are responsible for 95% of cerebral metastases. Metastases from lung cancer are the most frequent, representing more than 50% of cases. At the time of diagnosis, however, the primitive tumor site is unknown in a significant percentage of cases [2245].

The tendency to metastasize to the CNS is not the same for all types of tumor [400]. It is marked for melanoma and choriocarcinoma (which is a rare tumor), with a variable frequency of 39%–92%. Lung tumors come second (26%–46%), in the following order: adenocarcinoma, microcytoma, large cell carcinoma, and epidermoid carcinoma [585]. Breast tumors metastasize with a variable frequency from 15% to 20%. The risk is greater for stage 3 and 4 adenocarcinomas [3265] and tumors with few estrogen receptors [3314]. Hypernephromas metastasize to the CNS in 10%–25% of cases, while carcinomas of the gastrointestinal tract more rarely metastasize to the brain. There are, however, rarer tumors which have a relatively high frequency of craniospinal metastases, such as Ewing's sarcoma [1669, 3203].

The interval between the diagnosis of the primitive tumor and the development of cerebral metastases is variable, being on average 4 months for lung and 3 years for breast carcinomas, while hypernephromas and gastrointestinal carcinomas metastasize in later stages of the disease. It is controversial whether the incidence of metas-

tases has been increasing in the recent past. It seems to have increased for tumors which, following radio- and chemotherapy, are associated with a long survival, such as lung microcytomas [2461], soft tissue sarcomas, and sarcomas of bone [851].

Various types of primitive tumors may have preferential metastatic sites within the cranial cavity. Prostatic carcinomas, extending from bony lesions, involve the dura more frequently than the cerebral tissue. Lung carcinomas and melanomas, instead, metastasize more frequently to the brain. Adenocarcinomas of the breast develop leptomeningeal metastases as well as lung tumors and melanomas. It has to be noted that the meninges are more affected than the brain by noncarcinomatous metastases (melanoblastomatosis and meningeal sarcomatosis). Supratentorial localizations predominate (80%–86%), preferentially in frontal, temporal, and parietal locations. Regarding specific anatomic locations, the hemispheres rank first, while basal ganglia and brain stem (only 11% of cases) rank second. The posterior fossa is significantly overrepresented in pelvic (prostate or uterus) and gastrointestinal primary tumors [707]. Unusual sites include the pituitary, optic nerve, choroid plexus, and pineal gland. At the latter site 35 cases have been reported [3623]. In more than 60% of cases, metastases are multiple, with a greater incidence in autopsy than clinical material.

## 24.2

### Sex

In relation to sex, there is a prevalence in males, probably related to the higher incidence of lung tumors. The incidence was 9.7/100 000 for males and 7.1/100 000 for females in the United States [3593].

## 24.3

### Age

The incidence rate of cerebral metastases increases with age: 0.6 between 0 and 24 years, 5.3 between 25 and 44 years, 31.1 between 45 and 64 years, and 42.7 above 65 years [2609]. The average age lies in the sixth decade of life. The low incidence in the young is due both to the relatively lower frequency of solid tumors and their lesser tendency to metastasize to the CNS.

## 24.4

### Metastatic Pathways

Neoplastic cells reach the CNS mostly via the bloodstream; however, the incidence of brain metastases in clinical series does not correspond to that of neoplastic cells found at autopsy in patients bearing a malignant tumor, which is 100% for liver and brain [2449]. Malignant cells have to cross the capillary wall, i.e., the basement membrane. Populations of cells are not preselected on the basis of their adhesion properties to endothelial cells or any other features [893]. The preferential site of metastases

is at the border between the white and gray matter; the hypothesis is that malignant cells embolize in clusters of 100 and 200  $\mu\text{m}$  in size, which stop there [1299]. Metastases, which may also reach the CNS through bony and dura infiltration, are more frequently multiple. Single metastases represent up to 40% of cases involving primary lung tumors [2674]. Breast tumors have a high percentage of single metastases, over 40% [3471], more often in younger subjects, but in more advanced stages of the disease. Renal tumors usually metastasize after a long interval and are responsible of 10% of single metastases. However, these are unfortunately associated with metastases in other organs [1039]. Melanoma also may give rise to single cerebral metastases.

Usually, the prognosis even for single metastases is very poor, with a 2-year survival rate no greater than 15% [3665].

There are reported cases of extracerebral malignant tumors metastasizing to intracranial tumors, usually meningiomas or acoustic neurinomas. Metastases to neuroepithelial tumors are extremely rare [2326, 944].

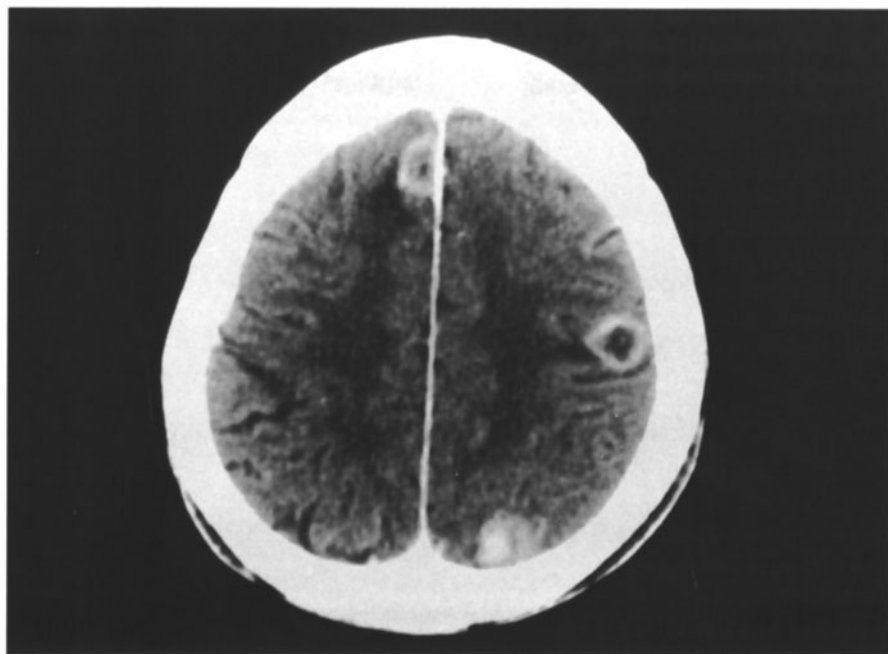
Most metastases are symptomatic, with or without evidence of the primary tumor. They can produce focal symptoms and a syndrome of increased intracranial pressure. The latter is due either to obstructive hydrocephalus or to perifocal edema. Focal symptoms are frequently associated with headache.

## 24.5

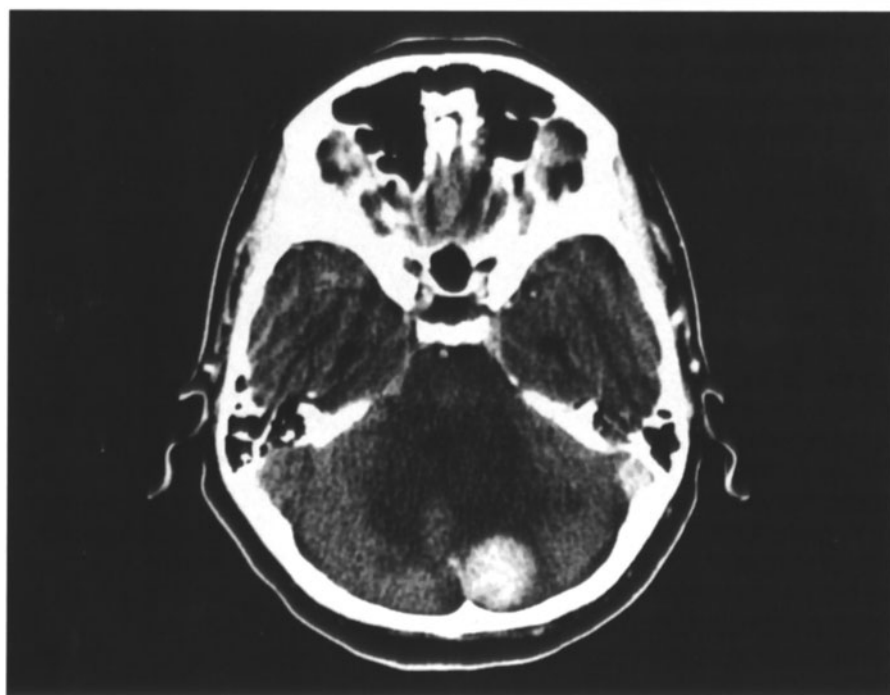
### Macroscopic Appearance and Imaging

Methods of choice for detecting metastases are computed tomography (CT) scan and especially magnetic resonance imaging (MRI). The general criteria are multiplicity, edema, and mass effect (Fig. 24.1a,b). Metastases are frequently seen at the transition between the white matter and the cortex. On T1-weighted images, they appear as hyperintense, sometimes with peripheral enhancement. On T2-weighted images, the lesion is hypointense and the perifocal edema hyperintense. With gadolinium, there is a good enhancement. Differential diagnosis must be made with a series of processes; this is most difficult when the lesion is solitary.

Metastases may be solitary, multiple, or diffuse (Fig. 24.2). Multiple or single metastases prevail in the neural parenchyma, while the widespread ones are more common in the meninges. The former have a nodular, roundish appearance with clear-cut borders. The cut surface is uneven, sometimes smooth; the color is usually grayish-red, but sometimes it is variegated because of regressive events, such as necroses, cysts, and hemorrhages. The consistency is soft, and in the unfixed state the tumor tends to disintegrate. The neural tissue is often edematous, both in proximity and at some distance from the metastasis. Sometimes, a single tumor nodule causes edema of the whole hemisphere [2974]. In relation to meningeal locations, it has to be remembered that in diffuse metastases, the macroscopic appearance is similar to that of meningitis. On the other hand, small metastases located in the dura mater may have a macroscopic appearance similar to that of meningiomas. In these cases, only the histological examination allows the underlying pathology to be ascertained.



a



b

**Fig. 24.1a,b.** Cerebral metastasis on computed tomography (CT). **a** Multiplicity. **b** Edema and mass effect



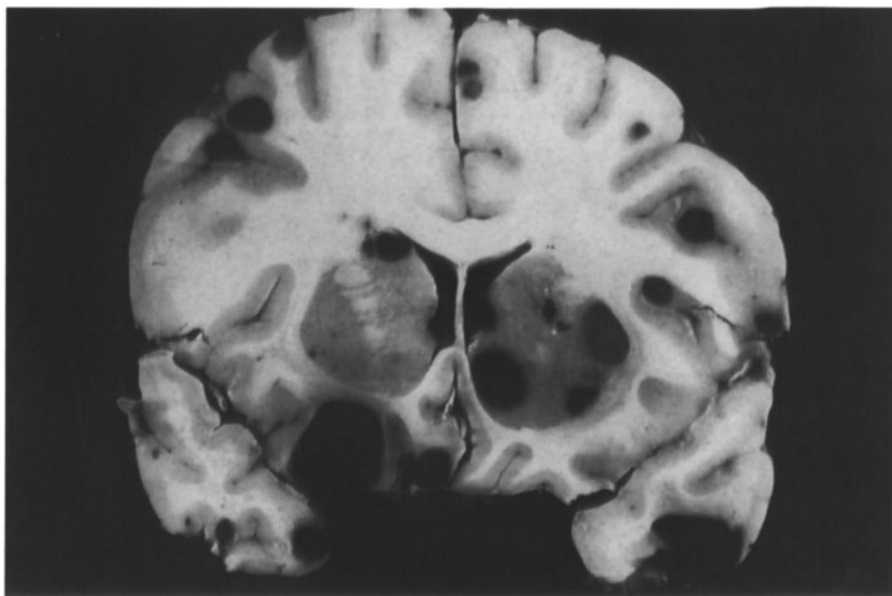


Fig. 24.2. Multiple metastases of malignant melanoma

## 24.6 Microscopic Appearance

Even though in a certain number of carcinoma metastases the histological appearance recalls that of the primary tumor, frequently, the recognition of the latter is impossible. This happened in 11.8% [3197], 25.5% [334], 35% [633], and 25% [3316] of cases. In general, from the various series, the order of frequency of tumor types is: lung carcinoma, breast carcinoma, carcinoma of unknown origin, melanoma, sarcoma, other tumors. In some series [3129], the proportion of metastases from the lung (55.2%) was followed by those from breast (14.3%); in others [941], lung and breast tumors are followed by renal carcinomas; in still other series, 95% of metastases [3687] were due to carcinoma of the lung, breast, kidney, gastrointestinal tract, melanoma, and choriocarcinoma.

The border with the surrounding nervous tissue may be clear-cut, but frequently there is diffuse neoplastic infiltration, or prongs and perivascular sleeves of tumor cells clearly demarcated from the neural parenchyma. In the nervous tissue, apart from edema, reactive gliosis may be marked and is represented predominantly by large hypertrophic astrocytes, clustered particularly in proximity to the metastatic tissue. Similar to what is observed in glioblastoma, endothelial proliferation is almost constantly present, and sometimes a rich network of sinusoidal-type vessels develops around the metastasis. The collagen stroma is usually scanty, contrary to what is observed in metastatic nodules located in organs rich in mesenchyma.

Amongst the more frequent regressive events, necrosis, processes of softening and liquefaction, cyst formation, and hemorrhages must be listed. Metastases are more or

less rich in mitoses and have a variable growth rate from one tumor to another, very often differing from that of the primitive tumor. Useful data have been obtained from the calculation of the labeling index (LI) after the administration of bromodeoxyuridine (BrdU): it may be higher than in the primitive tumor, indicating that the metastasis is growing more rapidly than the primary tumor itself [499].

## 24.7 Differential Diagnosis

In some cases, the differential diagnosis includes glioblastoma, lymphoma, or medulloblastoma and may be very difficult, except if one can identify the origin of the metastasis. The immunohistochemical demonstration of different antigens may be very useful (Fig. 24.3). Carcinomatous cells may have particular modalities of spread throughout the CNS and may, through direct subarachnoid diffusion or via the ventricles, give rise to carcinomatous meningitis.

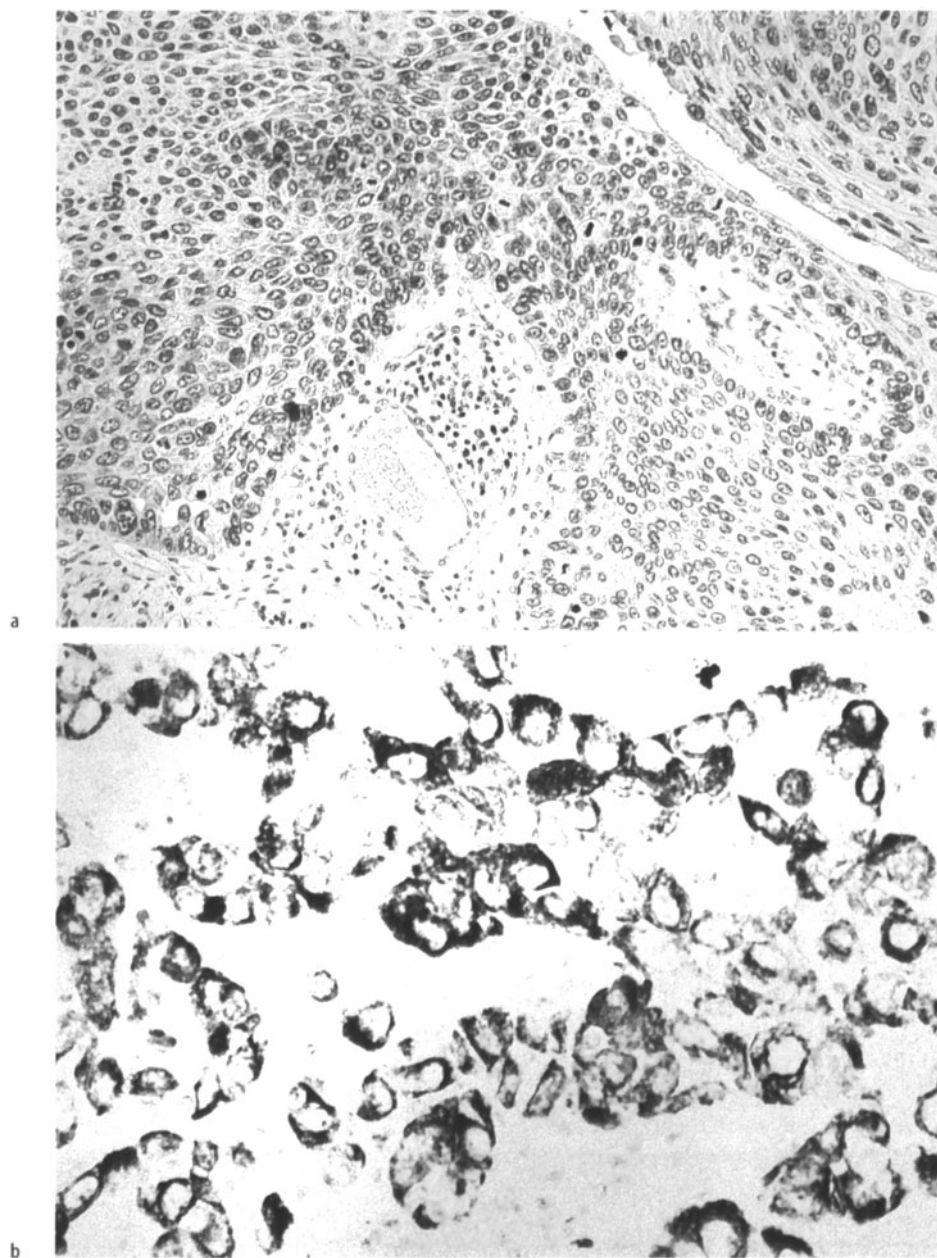
## 24.8 Prognosis and Therapy

The median survival of patients with brain metastasis is about 1 month without any therapy, increasing to 2 months with steroids and to 3–6 months with radiotherapy [2673]; at least 40% of patients die as a consequence of the systemic disease and not from brain metastases.

In patients with single unresectable or multiple brain metastases, and in patients with an active systemic disease, whole-brain radiotherapy (WBRT) with hypofractionated schedules (i.e., with single fractions of more than 200 cGy) is the standard treatment for palliation of symptoms [549]; in recent years, radiosurgery has been increasingly employed with similar results [3237].

In patients with solitary brain metastasis, localized to an accessible site and with an absent or controlled primary tumor, two randomized studies have shown that the combination of surgical removal and postoperative WBRT significantly improves the quality of life and median survival (40 weeks and 10 months, respectively) over WBRT alone (15 weeks and 6 months) [2568, 3532]. Long-term survival is more frequent after surgery and WBRT [3723]; in these patients, WBRT with hypofractionated schedules increases the risk of radiation-induced dementia [688]. It is now debated whether radiosurgery might be an alternative to surgical resection [2909, 2118].

In selected patients with recurrent brain metastasis, reoperation [255], brachytherapy with  $^{125}\text{I}$  [2677, 215], and radiosurgery [3155, 3156] may be of benefit. Chemotherapy is employed in chemosensitive tumors, such as small cell lung cancer, breast cancer, and ovarian cancer [367]. In metastatic spinal cord compression, steroids, surgical decompression, and/or radiotherapy are of benefit if an early diagnosis is made [2103].



**Fig. 24.3.** **a** Carcinomatous metastasis with many mitoses and hyperplastic stroma. H&E,  $\times 300$ . **b** Positivity for cytokeratin. PAP-DAB,  $\times 400$

## 24.9

### Carcinomatous Meningitis

This is being described more and more frequently, and in general it represents a late event in the course of the disease. However, with the improvement of treatment modalities, it has also been described in patients in full remission.

Setting aside the description of meningeal involvement in leukemia and in non-Hodgkin's lymphomas, carcinomatous meningitis has been described in lung and breast tumors [1984, 2500, 1135, 3417, 1741, 304]. The risk with small cell lung carcinoma has been calculated to be 25% at 3 years [2461, 2833]. This complication has been described in other malignant tumors [1444].

The invaded meninges are thickened and whitened, masking the blood vessels at the base of the brain. The cranial nerves may be involved, and nodules of different size may be found. Areas of thickening and nodules may also be found on the ependyma. Microscopically, the subarachnoid space is filled with neoplastic cells both at the cranial and spinal levels. Tumor cells ensheathing blood vessels penetrate the parenchyma and sometimes give rise to small deposits in the white matter, following the penetrating meningeal vessels. Neoplastic cells may cover the choroid plexuses [1299].

The pathogenesis of carcinomatous meningitis has not been completely elucidated. The tumor may reach the meninges by contiguous spread from the brain or spinal cord from the retroperitoneum through the intervertebral foramina, or via the hematogenous route [1741]. Ependymal nodules and perivascular sheets may be interpreted both in a causal role and as a consequence. The treatments of choice are intrathecal chemotherapy (methotrexate, cytarabine, thiotepea) and/or radiotherapy.

## 24.10

### Spinal Metastases

Spinal metastases are less frequent than intracranial ones, but not as rare as one would imagine. Metastases to the spinal cord are often missed, because less attention is focused on the spinal cord in comparison with the brain. The metastasizing tumor is usually a bronchogenic carcinoma. The spinal cord may be involved via the hematogenous route or secondarily from the leptomeninges.

More rarely, metastases may involve the choroid plexus, the optic nerve, the pineal body, etc.

## Biological Basis of Therapies

### 25.1

#### Radiotherapy

##### 25.1.1

##### Cellular Response to Ionizing Radiation

The primary target of ionizing radiation is the DNA, damage to which may occur as a result of either indirect and direct action. The former is typical of low linear energy transfer (LET) radiation, such as X- and gamma rays, that yield relatively little energy along their path (0.3–2 keV/ $\mu\text{m}$ ). The interaction with water molecules induces, through the release of fast electrons, the formation of free radicals ( $\text{OH}\cdot$ ,  $\text{H}\cdot$ ) which damage the DNA by extracting hydrogen atoms. Oxygen, if present at an adequate concentration, fixes the damage; under hypoxic conditions, the action of the so-called endogenous radioprotectors (i.e., sulfhydryl compounds), which are reducing agents, prevails. The direct action is typical of high LET radiations and charged particles (fast neutrons, protons, pions, etc.), with fast electrons directly damaging the DNA.

Lesions in the DNA can be classified into four types: (1) double-strand breaks, (2) single-strand breaks, (3) cross-linking of DNA to DNA or to other molecules, and (4) base damage. The repair is accomplished by different enzyme systems, such as ligases [1203] and nucleases. There is still uncertainty about the mechanisms by which ionizing radiation has varying lethal effects on the different cell types. As the intrinsic susceptibility of the DNA to radiation damage is similar for all cell types (viruses, bacterial, mammalian cells) [33], the DNA cannot be regarded as the sole target involved in the development of the radiation-induced lethality. The “DNA-membrane complex” essential for the beginning of cell replication and rich in lipids, which are particularly sensitive to radiation damage in the presence of oxygen, might be an important target in the induction of cell death [46, 1221].

From a radiobiological point of view, two types of radiation-induced cell death are known: interphase death and mitotic (reproductive death). The former consists of a direct killing of cells, obtainable generally with doses in excess of 10 000 cGy in nondividing cells (e.g., neurons), with the only exceptions being lymphocytes and oocytes, which are more radiosensitive. The latter is the cell death contingent upon the process of division (not necessarily the first division after irradiation) and, therefore, consists of a loss of the capacity to divide: It is obtainable with the lower doses employed in clinical radiotherapy both on neoplastic and most normal cells (e.g., bone marrow stem cells, endothelial cells, oligodendrocytes).

In culture, a cell which has retained its ability to divide indefinitely and produce a colony (clone) is defined as a clonogenic cell. The response of mammalian cells to various doses of ionizing radiation is graphically represented by a curve, with the dose plotted on a linear scale and the surviving fraction of cells on a logarithmic scale. With low LET radiation the dose-response curve is characterized by an initial shoulder, followed by a straight exponential part. The shoulder represents the fraction of cells whose damage has not been lethal and is repaired in few hours: It therefore expresses the ability to accumulate and repair the sublethal damage. By increasing the doses, the fraction of cells only sublethally damaged diminishes until a level is reached after which every dose increment induces a mitotic death in a constant number of cells, and the dose-response curves assumes an exponential slope. When a given dose of radiation is split into smaller doses ("fractionation") separated by an interval of time, a reappearance of a shoulder after every split dose is observed: This means that the number of cells able to repair the sublethal damage and to survive with fractionation is greater than the number of cells which would survive a same total dose delivered in one fraction. This phenomenon is exploited in clinical practice to minimize the late effects on normal tissues.

The exponential part of the curve is described by the value of  $D_0$ , which represents the dose required to reduce the number of clonogenic cells to 37% ( $1/e$ ) of their initial number, whereas the shoulder may be described by different parameters ( $n$ ,  $D_q$ , survival at 200 cGy):  $n$ , the extrapolation number, is the point found on the logarithmic scale by extrapolating the exponential slope;  $D_q$  represents the dose required to induce the sublethal damage). The in vitro radiosensitivity of cells from different human tumors seems to predict the clinical radioresponsiveness better if evaluated by means of parameters describing the shoulder other than those of the exponential slope [3629, 891, 2078]. Tumors with varying radioresponsiveness, such as medulloblastoma and glioblastoma, have similar values of  $D_0$  (135 vs. 143), whereas the differences are more significant when comparing the values of survival at 200 cGy (0.28 vs. 0.72).

The sensitivity of cells to low LET radiation varies according to the oxygen status and the cell cycle phase. Hypoxic cells are more radioresistant than fully oxygenated ones: This "oxygen effect" is measured by the oxygen enhancement ratio (OER), which is the ratio of the dose of radiation under hypoxic conditions to that under oxygenated conditions to produce the same biologic effect. OER values are usually 2.5–3; all normal tissues are considered as fully oxygenated. Cells are generally most sensitive in mitosis and most resistant in late S phase, whereas intermediate sensitivities are found in the  $G_1$  and early S phases [711, 1633, 1678].

Different studies [159, 2223, 1053, 2078] have shown that most glioma cells in vitro are quite radioresistant, similar to melanoma, and even more resistant than the normal glial cells [2431]. Dose-response curves are characterized by a large shoulder, reflecting an elevated capacity for the accumulation of sublethal damage [2105, 2701]. A certain variability has been found among different cell lines from the same tumors: some glioblastoma cells have displayed radiosensitivity values more like those of medulloblastoma cells than of melanoma [1053, 891, 2221]. Also, xenografts from glioblastoma into nude mice were not always radioresistant [3369]. Similar in vitro characteristics have been reported for cells of the 9L gliosarcoma of rat [1633].

In general, the inherent radioresistance of gliomas may depend on genetic mechanisms for producing DNA repair in sublethally damaged cells; for instance, protein kinase C (PKC) phosphorylates a plasma membrane protein that plays a role in radioresistance, and the administration of staurosporine, a potent PKC inhibitor, prior to radiation, attenuates the repair of damaged DNA in C6 cells [3783].

Fractionated irradiation, which is commonly employed in clinical practice, is influenced by four factors: (1) redistribution of the normal and tumor cells, (2) repair of the sublethal damage, (3) repopulation, and (4) reoxygenation. The rationale of radiation treatment is to exploit and, eventually, maximize the differences between tumors and normal tissues in relation to these factors.

The redistribution along the cell cycle consists in the fact that, after the first radiation dose, surviving cells, partially synchronized by their greater susceptibility in the more radiosensitive phases (i.e., M phase), tend to accumulate in  $G_2$  ("premitotic  $G_2$  block"). A precise timing of the second radiation dose in a radiosensitive phase would permit the killing of a greater number of cells. Anyway, during standard daily radiotherapy it is unlikely that any significant synchronization, resulting in a preferential depletion of tumor cells, will occur due to a redistribution in the cell cycle.

The repair of sublethal damage is generally completed within 1 h. It might be slower in tumor cells than in normal ones due to a reduced adhesion between cells or to a reduced ability of repair in hypoxic cells. Another type of radiation-induced damage is the potentially lethal damage (PLD), whose repair may occur more easily in noncycling and in starved cells.

Reoxygenation is of therapeutic relevance in neoplasias containing a high fraction of hypoxic cells (generally rapidly growing), which are more radioresistant. The first radiation dose kills a certain number of fully oxygenated tumor cells, which are removed, and as a result, a higher oxygen diffusion to the hypoxic cells will occur. This phenomenon may be the basis both for an increase in radiosensitivity and for regrowth.

### 25.1.2

#### Therapeutic Studies with Low Linear Energy Transfer Radiation on Experimental Brain Tumors

Both transplantable and autochthonous experimental brain tumors have been employed. The site of transplantation influences the response to radiation. The 9L gliosarcoma of rat is less responsive when transplanted subcutaneously than intracerebrally ( $D_{50}$ , 332 cGy vs. 180 cGy). This may be due to differences in the perfusion oxygenation of the tumor or to the number of cells repairing the PLD [3597, 3660]. Furthermore, dead cell removal is quicker subcutaneously [1809]. When employing intracerebral tumors in rats, the length of survival is the only parameter evaluable, as one cannot measure the size of the tumor before and after treatment or define the time of regrowth after radiation. Both with single and fractionated treatments a certain degree of dose-response relationship has been found; total doses of 3000, 4600, and 5750 cGy were more efficacious than doses of 2000 or 2300 cGy, whereas an increase of the dose per fraction did not improve the results [1043, 3303, 1291, 3661].

The transfer to clinical practice of data coming from experimental studies is limited by several factors, such as the frequent employment of single high doses, the different brain radiosensitivity and the short survival periods of animals, which does not permit an adequate evaluation of late effects.

### 25.1.3

#### Methods of Improving the Therapeutic Ratio in Radiotherapy of Brain Tumors

Most malignant gliomas, both clinically and experimentally, have been shown to be quite radioresistant [661], and therefore, various methods of improving the therapeutic ratio in their treatment have been explored.

##### 25.1.3.1

###### *Altered Fractionation*

Compared with a conventional treatment with daily fractionation, “accelerated fractionation” delivers the same total dose with more than one fraction per day, shortening the total treatment time. This technique might reduce tumor repopulation [3415], even though a too short interval between fractions might increase the risk of late damage [68, 321]. Hyperfractionation, i.e., the use of multiple small daily fractions in the same total treatment time, may permit the delivery of a higher total dose with an increase of the cell kill of the tumor. Nevertheless, it must be taken into account that the increase in tolerance of the nervous tissue (spinal cord of rat), by reducing the dose per fraction (from 200 to 100 cGy), is lower than expected theoretically [3509].

##### 25.1.3.2

###### *Brachytherapy*

Brachytherapy consists of a continuous low dose irradiation delivered by an interstitial implant of radioactive isotopes in the tumor. The potential advantages over the teletherapy are a continuous reoxygenation, which makes the neoplastic cells more susceptible to radiation injury; a modification of the distribution in the cell cycle with a tendency of cells to accumulate in  $G_2$  (more radiosensitive); a more effective repair of sublethal damage by normal tissues. Brachytherapy delivers doses higher than those of teletherapy to the tumor, provided it is relatively small, and the normal nervous tissue is better spared as the amount of radiation reaching it varies inversely with the square of the distance from the radioactive source. Some characteristics of gliomas render brachytherapy attractive: Most gliomas recur locally [1359], with only 5%–9% developing multiple lesions [510, 154], and slowly growing tumors (e.g., astrocytomas, oligodendrogliomas) seem radioresistant to low doses of external radiotherapy. Brachytherapy may be associated with teletherapy to increase the cell kill [3362, 214].

$^{125}\text{I}$  brachytherapy has been shown to be efficacious in different experimental brain tumors, such as the 9L gliosarcoma [1204], ASV gliomas [2517, 812], and xeno-



grafts of human gliomas in nude mice [1977]. Another method of delivering a high radiation dose on a small target by external beams is radiosurgery, which is well known in clinical practice [1202, 2632], but there are few experimental models [1746].

### 25.1.3.3

#### *Association with Chemotherapeutic Agents*

A cytotoxic drug may enhance the activity of radiotherapy by a number of mechanisms. It may interfere with the repair of the radiation-induced damage, permit a re-oxygenation of hypoxic cells by inducing a tumor shrinkage, and synchronize the cell population by killing a certain number of tumor cells. Nitrosoureas are the best known chemotherapeutic agents in the field of brain tumors. In vitro, both with human glioma cells [2223] and cells from the 9L gliosarcoma [3658, 698, 697] BCNU, and to a lesser extent CCNU, has been shown to potentiate the activity of radiation in a dose-dependent fashion, probably by means of an inhibition of the repair of sublethal damage. There was a certain variability among different cell lines, with some of them responsive only to combined treatments and not to single treatments. In animals, the combination of BCNU to radiotherapy has been demonstrated in a dose-dependent fashion to be superior to single treatments in improving both median and long-term survival; as in humans, a pulmonary fibrosis was evident [152, 3302, 3659, 3270, 3662]. Brachytherapy has been reported to be potentiated by BCNU [1204].

Radiosensitive properties have been attributed to bleomycin, hydroxyurea, cisplatin, carboplatin, and taxol.

### 25.1.3.4

#### *Radiosensitizers*

Malignant tumors, including brain tumors, are thought to contain a variable percentage of hypoxic cells responsible, at least in part, for the regrowth after conventional radiotherapy [1612]. A radiosensitization of hypoxic cells may be obtained through several mechanisms: an increase of oxygen diffusion by increasing the blood flow (triiodothyronine) or of oxygen pressure in the blood (hyperbaric oxygen); a direct cytotoxic effect (hyperthermia, nitroimidazoles); an oxygen-mimetic action in the presence of a low oxygen concentration due to a high electron affinity (nitroimidazoles). Among nitroimidazoles, metronidazole and misonidazole are the best studied: Being liposoluble compounds, they reach high concentrations in both tumors and normal nervous tissue. Studies in vitro and in vivo regarding the radiosensitizing action of misonidazole have yielded conflicting results [2746]. In recent years, new compounds were being investigated, either with greater radiosensitizing properties (pimonidazole, RO 03-8799) or with better pharmacokinetic characteristics (etanimidazole, SR 2508) [2421]. Nonetheless, a limiting factor of this therapeutic approach might be the limited size of the hypoxic fraction, reported both in some experimental [1912] and human [2467] gliomas.

Thiol-depleting agents reduce the cellular availability of sulfhydryl compounds, which favor the repair of damage from radiation-induced free radicals. The best known among these endogenous radioprotectors is glutathione (GSH), whose concentration in human brain tumors has been related to the degree of radiosensitivity [1801]. The intracellular level of GSH may be lowered by *l*-buthionine-sulfoximine (BSO), which inhibits GSH synthetase, thus inducing a low to moderate enhancement of radiosensitivity [2288]. The depleting action of BSO has been demonstrated in D-54MG human glioma xenografts in nude mice, with a selective depletion of tumor and not of normal nervous tissue [3211, 881]. In the same model, BSO potentiates the effects of brachytherapy [1977], provided that GSH depletion is almost complete. Furthermore, *in vitro* studies have suggested that BSO might potentiate the efficacy of nitroimidazoles [2288].

Another category of radiosensitizers is represented by halogenate analogues of pyrimidine, such as bromodeoxyuridine (BrdU) or iododeoxyuridine (IrdU), which are incorporated into the DNA of rapidly proliferating neoplastic cells to a much greater extent than in normal glial cells or neurons, because of their low mitotic index. Due to the high rate of hepatic degradation, an intra-arterial (intracarotid), an intraventricular, or a continuous intravenous infusion is required to achieve adequate cerebral concentrations [1162, 715, 1930].

Compounds able to reduce the energetic capabilities of neoplastic cells may interfere with the repair of radiation-induced potentially lethal damage, which requires energy. A certain efficacy has been reported *in vitro* on glioma cells for drugs interfering with glycolysis, such as 2-deoxy-2-D-glucose [796] and lonidamine [2538].

#### 25.1.3.5

##### *Hyperthermia*

The potential advantages of hyperthermia are several [717]. Radioresistant hypoxic, S phase, and G<sub>0</sub> cells are heat-sensitive; hyperthermia inhibits the repair of sublethal and potentially lethal damage induced by radiation. Higher temperatures might be obtained in the tumor than in the normal nervous tissue due to the differences in blood flow.

Studies on the nervous tissue's tolerance to heat (generated by ultrasound, radiofrequencies, and microwaves) have shown that the cerebellum is quite heat-sensitive, and the threshold for neuronal damage is about 43°C [337, 2926].

The heat sensitivity of cells from experimental brain tumors (9L, BT4C) was variable [2849, 641, 1292]; *in vitro*, the hyperthermia response for glioma cell lines has been shown to be similar to the responses of other cell lines with no correlations between radioresistance and heat resistance [2701].

A synergistic effect has resulted from the combination of hyperthermia (42.5°C) and radiation on 9L cells [2849, 1292]. Hyperthermia, both alone and associated with radiotherapy or chemotherapy or biologic modifiers, has shown a certain efficacy in several experimental brain tumor models *in vivo* [337, 2232, 1826, 2231].

### 25.1.3.6

#### *Photoradiation Therapy*

This mode of therapy consists in the systemic administration of certain compounds known as photosensitizers, which accumulate preferentially in neoplastic cells; when the photosensitizers are activated by light of an appropriate wavelength and intensity, they are able to destroy the cells [1624]. The primary damage might be to the vessel wall, with ischemic consequences. The best known photosensitizer is the hematoporphyrin derivative, whose efficacy was demonstrated in the 9L gliosarcoma [290], but it was limited by its inhomogeneous distribution and by the capability to penetrate into normal nervous tissue, thus inducing ischemic damage [3656].

New photosensitizers and more sophisticated systems of light delivery to deep tumors are currently being investigated [3657], but a limiting factor is represented by the nonuniform uptake of photosensitizers in individual patients [2511].

### 25.1.3.7

#### *High Linear Energy Transfer Radiation*

High LET radiation, compared with the low LET one, releases higher ionizing energy at the end of its path (so-called "Bragg peak"). The dose-response curve is characterized by a smaller shoulder (i.e., fewer cells able to repair the sublethal damage), and fractionation of the dose does not reduce its efficacy too much. In general, high LET radiation has a greater relative biological effectiveness (RBE), i.e., the ratio of the dose of a standard radiation such as X-rays of 250 keV, to the dose of a radiation of another type to produce the same biologic effect in the same biologic system. High LET radiation is less dependent for its efficacy upon the presence of oxygen (OER, 1–1.7) and cell cycle phases. Experimentally, fast neutrons have been shown to be equal, but not superior, to conventional radiation in prolonging the survival of rats bearing brain tumors [1043, 3270].

Encouraging results, both in vitro and in vivo, have been obtained with the boron neutron capture therapy (BNCT) [2635, 532]. It consists of the systemic administration of  $^{10}\text{B}$  which preferentially accumulates in neoplastic cells, followed by irradiation with fast neutrons; from the reaction, highly ionizing  $\alpha$ -particles are yielded.

### 25.1.3.8

#### *Radioprotectors*

An alternative method to improve the therapeutic ratio is that of selectively decreasing the sensitivity of normal tissue to the effects of radiation, without modifying the tumor sensitivity. The best known radioprotectors are the sulfhydryl compounds (cysteine, cysteamine and its derivatives), which act as free radical scavengers competing with oxygen in binding to the free radicals created by radiation. They protect fully oxygenated cells (such as normal cells) to a much greater degree than the hypoxic ones [2634]. WR-2721, a thiophosphate derivative of cysteamine, has been extensively studied: It is active in vitro on brain tissue [3765], but being highly hydro-

soluble, it does not cross the blood–brain barrier (BBB) [3492]. Higher concentrations of WR-2721 in the brain of animals seem to be obtainable by a direct injection into the cerebrospinal fluid (CSF) [3273] and by an intracarotid injection with previous opening of the BBB with hyperosmolar mannitol [1853]. A new radioprotector (omocysteine tiolactone) is under investigation [3275].

In recent years, the possibility that barbiturates (pentobarbital) may reduce cerebral radiation toxicity [2489, 2499] by a mechanism still unknown has been suggested.

## 25.2 Chemotherapy

### 25.2.1

#### General Concepts

A drug is effective against a tumor if neoplastic cells are sensitive to it and if the drug reaches the site of action at a cytotoxic concentration for an adequate period of time. Several factors may therefore influence the response to chemotherapy: the mechanism of action of the drugs and their timing, correlated to the kinetic parameters of the tumor; the intrinsic chemosensitivity of neoplastic cells; and the drug delivery, which, for brain tumors, is strongly influenced by the existence of the BBB [3143, 956]. Chemotherapy agents are either cycle specific, i.e., effective only in some phases of the cell cycle, or non-cycle specific, i.e., effective whatever the phase. Some drugs, e.g., BCNU, are non-cycle specific, but they are more effective during DNA synthesis. A single agent may seldom be effective against all neoplastic cells, for several reasons: Tumors may be composed of cells with varying chemosensitivity; a tumor cell line, initially sensitive to a drug, may become resistant after several exposures (e.g., methotrexate); the volume reduction obtained either with a non-cycle-specific agent or with surgery or radiotherapy induces a shift of tumor cells from the nonproliferating ( $G_0$ ) to the proliferating compartment, thus increasing the growth fraction. Polychemotherapy, i.e., the association of drugs with different mechanisms of action, relies on these premises. For instance, if a non-cycle-specific agent is used first, a cycle-specific agent (e.g., 5-fluorouracil, methotrexate) should be used during the following phase of regrowth. Some drugs (e.g., vincristine, VM26) may be used to synchronize the cell cycle to accumulate the greatest number of cells in a phase sensitive to a cycle-specific agent administered subsequently. With polychemotherapy, it is also possible to associate drugs with different toxicities (e.g., nitrosoureas, which are myelotoxic, and vincristine or VM26, whose myelotoxicity is much lower), so that every agent may be administered at a full dose.

### 25.2.2

#### Chemosensitivity and Chemoresistance in Brain Tumors

The existence of a heterogeneity in the sensitivity to various chemotherapy agents (e.g., BCNU, cisplatin, procarbazine, vincristine, doxorubicin, a-difluoromethylor-

nithine) for clones deriving from both human malignant gliomas [1754, 963, 3138, 3768, 277, 278, 160] and experimental brain tumors [2836, 3756, 3579] is well established. There are differences in the chemosensitivity among tumors and among different regions of the same tumor [3143]. BCNU-sensitive cells are usually hyperdiploid, whereas BCNU-resistant ones show diploid karyotypes [3137] and might be the dominant cell type in the recurrent tumors [3136]. The exposure to low drug doses of BCNU might facilitate the development of highly resistant clones [3143]. Different mechanisms may underlie the drug resistance, being different in different tumors and for different drugs, and some of them might act simultaneously. A reduced uptake is known for methotrexate [420], whereas an increased active efflux has been shown in lines from human gliomas for vincristine [1564] and in C rat glioma for doxorubicin and ACNU [3579, 3758]. The existence of an increased active efflux mechanism in cell lines from 9L gliosarcoma is uncertain [3143, 3758]. The drug resistance to vincristine and doxorubicin is a multidrug resistance (MDR) [3085, 2158]: In cells deriving from both noncerebral and cerebral tumors, the MDR seems correlated with high levels of a membrane P glycoprotein [3085, 2159], which could bind to antineoplastic agents and thrust them out of the cell. The development of a MDR seems correlated with an increased expression and amplification of either a gene (MDR-1 gene) or a family of genes which codify this P glycoprotein [1599, 3110]. An increased expression of MDR-dependent mRNA has been detected in vincristine-resistant cell lines from human gliomas [2158]. The MDR-1 gene has been detected in normal brain and benign and malignant tumors, while P glycoprotein can be present in tumor blood vessels even though it is not demonstrable in tumor cells [2370]. Calcium-blocking agents (i.e., verapamil, nifedipine), which specifically compete with some cytostatic drugs for binding the P glycoprotein, or inhibitors of the protein kinase C (calphostin C), which phosphorylates the P glycoprotein, may reduce the efflux of the drugs from multidrug-resistant cell lines derived from human astrocytic gliomas [3758, 2158, 1743, 2160].

Other mechanisms involved in the resistance to chemotherapy agents are either an alteration of the intracellular distribution and/or a transformation of the drug [3085] or an activation of compensatory metabolic pathways, e.g., an increase of dihydrofolate reductase synthesis for methotrexate [420].

In recent years studies have been devoted to cellular mechanisms of repair of damage from alkylating agents, particularly chloroethylnitrosoureas (CENUs). One of the reaction sites between these compounds and DNA is the O<sup>6</sup>-position of guanine. Repair from this damage is based on the action of the enzyme O-alkylguanine DNA alkyltransferase (AGT), which moves the alkyl group formed in the DNA to a cysteine residue contained in its sequence. This reaction restores the guanine in DNA and inactivates the alkyltransferase: Thus, a *de novo* synthesis of the enzyme will be necessary. GATase is present in cell lines and xenografts from human gliomas, in surgical specimens from several brain tumors (especially meningiomas and neurinomas), and in normal nervous tissue [3670, 3080]: The amount of this enzyme is variable but generally lower in cell lines than in xenografts or in resected tumors, and the same is true for normal nervous tissue compared with brain tumors. It has been hypothesized that the GATase activity level might influence the cell chemosensitivity to alkylnitrosoureas, including chloroethylnitrosoureas [2367]. Recent data seem to confirm this hypothesis: a BCNU-resistant cell line from the 9L gliosarcoma (BTRC-

19) has shown high levels of GATase [1970]; an inverse ratio between the GATase level and the chemosensitivity to BCNU has been found in xenografts from human astrocytic gliomas [3080]; low levels of AGT activity have been found in five out of five chemosensitive human oligodendrogliomas [2464]. An increase of *O*<sup>6</sup>-alkyltransferase activity in cell cultures and xenografts from brain tumors after radiotherapy has been reported [2835]. If a radiation-induced increase of BCNU resistance is confirmed, the administration of CENUS would be more effective before, and not after, radiotherapy.

A series of compounds have been synthesized and tried as inactivators of AGT: *O*<sup>6</sup> benzylguanine (BG), a lead compound, 8-ara- and 8-bromo-derivates of BG, and the 5-nitroso- and 5-nitroderivates of 2,4-diamino-6-benzoxypyrimidine [277, 278, 2595].

A trend towards decreased AGT activity and increased susceptibility of procarbazine-treated xenografts in brain tumors with p53 mutations has been reported and supports the hypothesis that mutational inactivation of p53 can enhance chemosensitivity [2906].

GSH binds to intermediate products of CENU catabolism, thus reducing their alkylating activity, and may prevent damage from several chemotherapeutic agents. A mild correlation between GSH content, GSH synthetase activity, and BCNU resistance has been shown in cell lines from human gliomas [37]. BSO, which depletes the intracellular glutathione content, seems to increase the cytotoxicity of BCNU in resistant cell lines from human gliomas [36] and of melphalan in xenografts from medulloblastoma [969].

Several assays have been developed to test the chemosensitivity of brain tumors in vitro [1679].

The colony-forming assay (CFA) measures the effect of a drug upon stem cells, i.e., cells that maintain their ability to divide. It has several limitations: Noncycling cells, which may potentially enter the cycle, are sometimes not measured, and a high percentage of stem cells in gliomas may actually be in a resting state (*G*<sub>0</sub>); a low cell density does not occur in vivo; many neoplastic cells do not form colonies, whereas a growth of normal tissue is possible. Radiolabeled precursor inhibition assays measure the drug-induced inhibition of labeled precursors of DNA, RNA, and protein synthesis (e.g., thymidine, uridine, or amino acids). The main limitation of these assays is the possibility of measuring only an inhibition of synthesis, which may be a temporary effect, and not the extent of cell death. Microcytotoxicity and growth inhibition assays measure chemosensitivity by counting viable cells, one or several passages after drug exposure. The advantage of the short time needed for the test is hindered by a lack of sensitivity due to the large amount of drug required. Organ culture and multicellular tumor spheroid assays are based on the morphologic evaluation of tumor growth. They more closely reproduce in vivo conditions (e.g., problems of drug penetration), but they are considered less reliable. The sister chromatid exchange (SCE) assay measures the drug-induced metaphase SCE. For detecting the effects of low drug concentrations, it is rather sensitive, but it does not directly measure cell kill.

Several authors employing in vitro assays have retrospectively correlated the chemosensitivity with clinical outcome [1756, 287, 2838, 2836, 3422]. In vitro resistance to BCNU generally predicts clinical resistance, whereas in vitro sensitivity is asso-

ciated with a clinical response in only 65% of patients. A sensitivity to BCNU has been reported as more frequent in young patients with longer survival expectations. Studies in which chemotherapy is prospectively selected on the basis of in vitro results are in progress, while the true clinical impact of drug testing remains to be defined.

The regional heterogeneity of malignant gliomas remains a limiting factor for all in vitro assays; however, more problems are to be solved before they are considered reliable in planning an adequate chemotherapy for individual patients: the use of a drug concentration reproducing tumor concentrations in vivo; the use of a time exposure adequate for both cycle and non-cycle-specific drugs; the possibility of testing single agents, which require metabolism before they are effective, and multiple agents.

### 25.2.3

#### Drug Delivery to Brain Tumors

Several factors determine the concentration in the nervous tissue and in brain tumors of a systemically administered drug [1165]. These are the plasma level of the free drug in relation to time, the BBB permeability, and the local brain flow rate. After the systemic administration of a drug, the time needed to achieve a peak in the serum depends on the modalities of administration; the concentration thereafter diminishes because of redistribution, elimination, and catabolism. The amount of drug reaching the nervous tissue depends on the plasma concentration peak and its duration: A high steady state concentration may optimize drug uptake, whereas a rapid clearance makes it minimal. The BBB permeability to the drug is directly correlated with its lipophilicity, as determined by its octanol/water partition coefficient, *p*. Highly lipid soluble compounds (e.g., nitrosoureas) may rapidly diffuse through the BBB, and the only limitation to their distribution in the nervous tissue is the local flow rate, whereas water-soluble compounds have a very limited penetration in the nervous tissue. Recent studies utilizing quantitative autoradiography in experimental brain tumors [268] and positron emission tomography (PET) in human brain tumors [1510, 345] have shown that the breakdown of the BBB may be variable within large metastatic lesions and malignant gliomas, and in some areas, the BBB is almost intact. Most often, there is a breakdown in the BBB with a reduction of blood flow, but in peripheral areas, the breakdown is minimal, and the blood flow is nearly normal. In the brain adjacent to tumor (BAT), the capillary permeability may sometimes be reduced compared with normal nervous tissue [1928]. In very small tumors and in low-grade gliomas, the BBB and flow rate are almost normal [1165].

For drugs which cannot cross an intact BBB (e.g., water-soluble compounds), the only possibility of access to a brain tumor is that of a passive diffusion from areas with a breakdown of the BBB, but this mechanism seems to have a limited cytotoxic effect [1926]. Problems of drug distribution may exist even in the presence of a breakdown of the BBB [1165]. The distance between capillaries is often increased in brain tumors, thus reducing drug and oxygen diffusion, with many cells remaining in  $G_0$ , and thus not sensitive to cycle-specific agents; both normal tissue around the tumor and the CSF act as a diffusion sink, reducing the cytotoxic concentration of

the drug inside the tumor; and the perivascular drainage is effective in brain tumors. Except for the nitrosoureas, most antineoplastic drugs do not have the physicochemical characteristics required to diffuse through the BBB; therefore, they do not reach an adequate concentration in the nervous tissue after intravenous administration, and this fact has led to the search for new modalities of drug delivery and for new drugs.

Among new therapeutic modalities, some are meant to increase the blood concentration of the drug, by administering very high doses or by locoregional, intraarterial administration. Methotrexate, which is water soluble, can scarcely diffuse through the BBB at conventional dosages [3141], but its uptake is significantly increased if it is administered at high doses continually (over 24 h) [420] (in association with leucovorin rescue to minimize the cytotoxic effects on normal tissue). High doses of drugs with hematologic toxicity (e.g., BCNU) may be administered intravenously in association with autologous bone marrow transplantation [900] or hematopoietic growth factors (e.g., granulocyte colony-stimulating factor, G-CSF; granulocyte-macrophage CSF, GM-CSF).

Intra-arterial (carotid and vertebrobasilar) administration of a drug [3313] leads to higher concentrations of the drug in the tumor, as confirmed in PET studies [879], with minimal systemic toxicity. Many drugs have been tested, e.g., BCNU, PCNU, HeCHU, ACNU, antimetabolites, alkylating agents, plant alkaloids, cisplatin, carboplatin, antibiotics. The major risk is represented by delayed neurotoxicity, especially when employing liposoluble drugs (i.e., nitrosoureas) and superselective infusions distal to the ophthalmic artery [929, 167, 324]. Neurotoxicity has been related to the drug itself, to the ethanol used as a diluent, to the association with radiotherapy, and to a streaming phenomenon [2950] determining a dyshomogeneous distribution of the drug, with the risk of neurotoxic concentrations in normal areas.

As a consequence, intra-arterial chemotherapy is not suitable for adjuvant treatment of brain tumors, but it may be employed as an experimental therapy in tumors recurrent after conventional therapies. New compounds are now under investigation, such as RMP-7 (which increases the BBB permeability), O<sup>6</sup>-benzylguanine (see above), and melphalan [2155, 1827].

Modalities to circumvent the BBB have also been developed.

### 25.2.3.1

#### *Intra-Cerebrospinal Fluid and Interstitial Chemotherapy*

The administration of drugs directly into the CSF by a lumbar or a ventricular route allows a high concentration of the drug to be reached in the CSF with a lower dosage. The drugs most often used are methotrexate, thiopeta, cytosine arabinoside. Drug diffusion through the BBB is minimal, except for a few areas [1166], and some risks must be considered, such as erroneous injection into the subdural and extradural space, infections and neurotoxicity. The administration of the drug directly into the tumor (interstitial chemotherapy), employing biodegradable polymers with a slow release of drugs such as BCNU, taxol, and camptothecin is under investigation [3603, 3632].



### 25.2.3.2

#### *Transient and Reversible Blood–Brain Barrier Modification*

The so called osmotic opening of the BBB is based on the observation [2732] that the rapid intracarotid administration of a water soluble hyperosmolar agent, e.g., mannitol, determined a transient and reversible opening of the BBB (within 4 h), with a sevenfold increase of the permeability to methotrexate [2733]. The increased capillary permeability seemed to depend on an osmotically induced shrinkage of the endothelial cells with a partial opening of the tight junctions; their progressive rehydration restored the integrity of the BBB. Several antineoplastic drugs (cisplatin, adriamycin, bleomycin, 5-fluorouracil) showed neurotoxicity in dogs and rodents, when administered after osmotic opening of the BBB, whereas methotrexate, cyclophosphamide, and carboplatin seem to be relatively safe [2411, 3684]. Data deriving from the application of this modality in experimental brain tumors are contradictory: according to some authors [2410], there is an increase of the capillary permeability in the tumor and peritumoral tissue, while according to others [3613, 1175], there is an increase of permeability only in normal nervous tissue (brain cortex, corpus callosum). These discrepancies could be partially ascribed to the different responses of microvessels in different experimental tumors [1285]. Nonetheless, the osmotic opening of the BBB has been recently questioned [912], because it is aspecific and allows the diffusion of many hydrophilic endogenous compounds (bradykinin, peptides, and amino acids) which may be neurotoxic. Because of these uncertainties, it seems preferable to conduct more experimental studies before this modality is extensively utilized in humans [1175].

Brain irradiation at low doses can transiently increase the vascular permeability in the nervous tissue of rats [1927, 2633, 709], but not in experimental brain tumors, and the same seems true at high doses [3274, 709].

### 25.2.3.3

#### *Carrier Systems and Liposomes*

Experiences with these two modalities are still in an early phase.

The diffusion of some drugs (especially water-soluble ones) through the BBB would be increased if their structural similarities with other compounds normally carried through the BBB by active carrier systems could be exploited. For instance, melphalan has been shown to have some affinity for the large neutral amino-acid carrier system [1165, 2781] and sarcosinamide chloroethylnitrosourea has some affinity for the colamine carrier system [3210]. It is possible to develop real carrier drugs, i.e., lipophilic compounds, which could transiently bind a polar agent and diffuse with it through the BBB. Liposomes are artificial lipid vesicles diffusing through the capillar endothelium, and they may incorporate and carry several drugs, enzymes and monoclonal antibodies [329]. When carried by liposomes, an increased cytotoxicity for methotrexate on human glioma cells in vitro [1693] and for doxorubicin in an experimental sarcoma of the brain [3190] has been reported. However, in an experimental model of brain metastasis from melanoma [2970], an accumulation of liposomes in the tumor and in normal nervous tissue with significant toxicity from embolism has been shown.

The search for specific antineoplastic agents to be used in brain tumors continues in two directions [1166]: (1) the synthesis of new lipophilic compounds; (2) an increase of the liposolubility of already known agents. SHM (spirohydantoin mustard), AZQ (aridinybenzoquinone), estramustine, fotoemustine, etc.) are drugs belonging to the first group, whereas drugs derived from the nitrosoureas BCNU and CCNU (e.g., MeCCNU, PCNU, ACNU), from methotrexate (trimetrexate), and from chlorambucyl (prednimustine) belong to the second group.

## 25.3 Immunotherapy

Two different immunotherapeutic approaches are possible: (1) the utilization of monoclonal antibodies as either cytotoxic agents or carriers of chemotherapeutic agents and radionuclides; (2) the stimulation of the immune response against the tumor.

The possibility of using monoclonal antibodies as cytotoxic agents against tumor cells was experimentally confirmed in vivo and in vitro [1687, 2270, 2801, 435]. These data suggest that adequate monoclonal antibodies against tumor cells may have a therapeutic role for solid tumors in man.

In 1905, Ehrlich first suggested employing antibodies as carriers of chemotherapeutic agents, but this approach became suitable for immunotherapy only with the use of monoclonal antibodies. Highly specific monoclonal antibodies may be used as carriers of radionuclides, toxins or drugs [317, 3663, 1223]. Toxins from both plants and bacteria (ricin, abrin, gelonin, diphtheria toxin and toxin from *Pseudomonas aeruginosa*), drugs, (chlorambucil, methotrexate, daunomycin, and neocarzynostatin), and many radionuclides have been successfully conjugated with antibodies.

Monoclonal antibodies targeted to epidermal growth factor receptor (EGFR), platelet-derived growth factor (PDGF), tenascin, and CS proteoglycan are under investigation in human malignant gliomas and neoplastic meningitis [253, 2804].

These techniques present, however, many limitations in their use. The first one depends upon the incomplete specificity of monoclonal antibodies against brain tumors, with a cross-reaction with normal tissue. The amount of antibodies reaching the target depends upon several factors, e.g., tumor vascularization, capillary permeability, blood flow rate, and extracellular fluids [382]. Antibodies may easily reach the deep portion of the tumor, because of the breakdown of the BBB, but the same is not true for the periphery of the tumor, which is actively proliferating. Therefore, agents which may modify the BBB permeability to antibodies [2409] might be needed. Another major limitation derives from the antigenic heterogeneity of malignant gliomas [382], so that a monoclonal antibody may only bind to a limited proportion of the tumor cells. This low sensitivity is a consequence of the high specificity of monoclonal antibodies, so that better results might be obtained if different antibodies binding to different tumor antigens were given at the same time. Finally, the possibility of an anaphylactic reaction, due to repeated administrations of immunoglobulins, must not be neglected.

The second approach to immunotherapy is a modification of the cell-mediated immune response against the tumor. Stimulation of the immune response may be ob-

tained with either lymphokines, e.g.,  $\gamma$ -interferon and interleukin (IL)-2, or activated lymphocytes [1272]. In the immune response,  $\gamma$ -interferon may stimulate the expression of class II HLA-DR antigens in macrophages, thus increasing the antigen presentation to T lymphocytes. It has been observed that astrocytes and glioma cells may express HLA-DR antigens and that  $\gamma$ -interferon may increase the expression of these antigens [1050, 2641]. Moreover, these cells may present antigens to T lymphocytes in vitro. One may hypothesize that the administration of  $\gamma$ -interferon also stimulate the in vivo immune response to gliomas, increasing the presentation of tumor antigens to T lymphocytes that infiltrate the tumor [682]. IL2 might be used because it stimulates T cell proliferation, thus increasing the number of activated lymphocytic populations. Another technique involves the administration of specifically activated autologous lymphocytes. T lymphocytes cytotoxic for tumor cells might be administered, as it is now possible to expand in vitro lymphocytic clones activated by tumor cells [3745].

The existence of specific lymphocytic populations has been shown in human gliomas, which are significantly more active than peripheral blood lymphocytes and kill allogenic and autologous tumor cells. The possibility of expanding these populations to a sufficiently high number and injecting them into the tumor seems attractive. Also, the so-called LAK cells, autologous killer cells activated by lymphokines, may be useful in the immunotherapy of gliomas [1488].

A major obstacle to these techniques for immunotherapy is the presence of factors that decrease the immune response against gliomas. Besides the existence of circulating immunoglobulins and antigen-antibody complexes that may inhibit the immune response [3208], a factor that may antagonize the activity of IL-1 and IL-2 has been isolated in cultures of glioma cells [926]. This factor, which has been recently identified as transforming growth factor (TGF)- $\beta$ 2 [675], inhibits the IL-2-dependent T lymphocyte proliferation and the production of cytotoxic T lymphocytes in culture and of LAK cells [1822]. Antibodies against this "glioma-derived T cell suppressor factor" to antagonize its immunosuppressant effect might be tried.

## 25.4 Biologic Therapies

Drugs such as trapidil (a PDGF-blocking agent) or suramin (an inhibitor of the binding of PDGF, EGF, and tumor growth factor  $\beta$  to their receptors) are under investigation as a form of anti-growth factor therapy [2928].

Differentiating agents are designed to induce tumor cells to differentiate toward more mature phenotypes; phorbol esters, cyclic adenosine monophosphate (cAMP), and retinoids have been most extensively studied [1971].

Antiangiogenesis is another therapeutic approach [899], employing several new agents which interfere with endothelial cell proliferation. Platelet factor 4 (PL-4) must be directly injected into the tumor; as it rapidly binds to the endothelium, high systemic levels cannot be reached. TNP-470 (a synthetic analogue of fumagillin) and thalidomide are suitable for systemic therapy. The latter, in particular, has a favorable pharmacologic profile, including a relatively long serum half-life, excellent bioavailability, and low toxicity (except for in pregnant women); thus it is promising for long-term cytostatic (rather than cytotoxic) therapy.

Gene therapy is based on a targeted transfer of genetic material (DNA) with the purpose of effecting a change in tumor growth [2948]. The two major components of gene therapy are the delivery system (vectors) and the therapeutic gene (transferred gene or transgene). Brain tumors seem to represent an excellent model for this form of therapy, as they are relatively localized tumors and the CNS is a relatively immunoprivileged site, and any immune response to the vector or to the transgene would be attenuated.

Vectors may be viral or nonviral. The basic concept behind viral vectors is to exploit the natural life cycle of viruses, i.e., to infect eukaryotic cells and express foreign genes within infected cells. Most commonly employed viral vectors are retroviruses, adenoviruses, and herpesviruses. A nonviral method of transferring genetic material may be that of encapsulating the foreign DNA in lipophilic liposomes, which could be potentially safer, less immunogenic, and without limitation as to the size of the DNA. Therapeutic genes may be cytotoxic genes, growth regulatory genes, and immunogenic genes.

The approach to gene therapy of brain tumors has currently mainly focused on the transfer of cytotoxic genes, in particular herpes simplex virus (HSV)-1 thymidine kinase (TK) gene [617, 1818, 2279]. TK has the ability to phosphorylate a number of nucleosides such as ganciclovir (GCV). TK of normal cells (neurons, glia) does not phosphorylate GCV. Only cells that have been transduced by the HSV-1 TK gene are susceptible to cell killing following exposure to GCV. In experimental models, the HSV-1 TK gene was inserted into murine fibroblasts by retrovirally mediated gene transfer and the transduced cells were stereotactically injected into rats bearing intracerebral gliomas; at this point, the retroviral vectors infected the adjacent replicating tumor cells, becoming susceptible to treatment with GCV. Herpesvirus vectors might be used in another setting. For example, the genetically engineered HSV-1 mutant *dlspk* completely lacks TK activity and, as a result, cannot replicate in nondividing cells, such as neurons and normal glia. Hence such a virus preferentially divides in and proves cytopathic to neoplastic cells in the brain. In cell culture and in xenografts in the nude mice, it has been shown to efficiently kill gliomas and other CNS tumor types [2138]. Cells altered by gene insertion can also be used as vectors for therapeutic strategies directed at growth factors and growth factor receptors. In rats with C6 gliomas, the injection of tumor cells transfected with the gene for antisense insulin-like growth factor I (IGF I) produced regression of tumors [3461]. Antisense oligonucleotides have also been employed [3461].

A pattern of wild-type p53 loss of function and mutant p53 activation has been observed in association with the MDR gene; thus it is conceivable that the use of gene insertion to increase the amount of wild-type p53 activity might inhibit neoplastic growth, reverse the neoplastic phenotype, and increase sensitivity to both chemotherapy and hyperthermia [2928].

## Effects of Treatment on Brain Tumors and Normal Nervous Tissue

### 26.1

#### Effects of Radiotherapy and/or Chemotherapy on Human Brain Tumors

The effects of radiotherapy and chemotherapy on malignant gliomas have been studied extensively [3688, 1052, 1519, 391, 3014, 3015, 3017, 1205]. Since they are not specific, it is difficult to separate them from those developing spontaneously in the tumor during its natural course. An example is glioblastoma central necrosis. The frequency of the changes depends on the material available for study, biopsy or autopsy, time elapsed between treatment and death, and radiation dose. Macrophagic areas, monstrous and giant cells (Fig. 26.1), atypical mitoses and bizarre astrocytes are maximally represented at a short distance from the irradiation and, therefore, might be considered as short-term effects. Vessel wall changes, e.g., hyalinization and fibrinoid necrosis, increase both with the radiation dose and the distance from treatment. Also, the disappearance of morphologic features typical of active growth such as endothelial proliferations and mitoses, parenchymal mitoses and circumscribed necroses with pseudopalisading can be attributed to radiotherapy. All these features reappear along with the tumor regrowth that most frequently happen for glioblastomas between 6 and 12 months after doses of about 6000 cGy [3017, 393]. Interesting but not specific are the morphologic patterns of regrowth: an overgrowth of a population of small anaplastic cells may take place and tumor repopulation may start again both from cells in the brain adjacent to the tumor (BAT) and from cells close to the central necrosis. The tumor builds up new vessels from those of the normal nervous tissue already damaged by irradiation, as demonstrated by the occurrence of endothelial hyperplasia in vessels with fibrous-hyalin degeneration of the wall. In long term survivors, more commonly after 1 year after the end of radiotherapy, a population of fibroblastic-like cells develops from thickened hyalinized vessel walls [3031]. These cells have been interpreted as an expression of a sarcomatous transformation, even though true fibrosarcomas from irradiated glioblastomas have never been observed, perhaps because of the associated short duration of survival.

Morphologic changes produced by chemotherapy on malignant gliomas are hardly distinguishable from those produced by radiotherapy. An increase of monstrous and giant cells and, less frequently, of nuclear hyperchromasia and nuclear-cytoplasmic inclusions after treatment with different drugs are reported [1521].

In all autopsy series of malignant gliomas treated with radiotherapy after surgery [391, 3014, 3015] or intra-arterial chemotherapy [2840], there are patients with no sign of tumor regrowth but with severe damage of the normal nervous tissue.

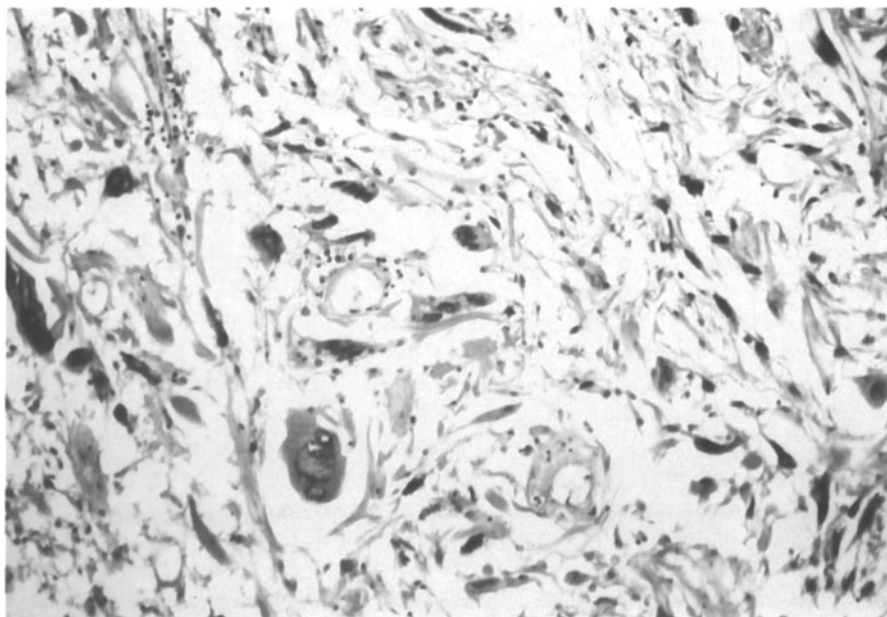


Fig. 26.1. Monstrous cells in irradiated glioblastoma. H&E,  $\times 400$

Very few data are available on the effects of radiotherapy on well-differentiated astrocytomas. In a personal series [3019], astrocytomatous areas of glioblastomas were studied, and the only change was chronic edema. In one case, small necrotic foci were found, probably representing small anaplastic foci sterilized by radiation. In the case of brain tumors more radiosensitive than gliomas, such as medulloblastomas, germinomas, lymphomas, leukemias, and metastases, an almost complete sterilization of the neoplastic cells may sometimes be observed.

## 26.2

### Effects of External Radiotherapy on the Human Brain

Adverse effects of external radiotherapy on the normal human brain may be divided into three types according to the latency period [3157, 1908]: acute, early delayed, and late delayed. Acute effects occur during irradiation and clinically are variably characterized by headache, nausea and vomiting, somnolence, temperature elevation and an exacerbation of neurologic symptoms and/or signs, being transitory and reversible with steroids. The acute syndrome is more frequent when the previous neurological status of patients was poor and when treatments with high doses per fraction (more than 2 cGy) are used. No pathologic data are available on this syndrome.

Early delayed effects appear between 2 weeks and 4 months after irradiation, with a variety of reversible neurologic symptoms, and the incidence may approach 25% [802]. Autopsy cases are exceptional [1851, 1852, 2298]. The neuropathologic picture

consists of multiple, punched-out foci of demyelination, perivascular infiltration of lymphocytes and plasma cells, glial reaction, and absence of degenerative changes of vessel walls.

Among late delayed effects, cerebral radionecrosis is the best known pathologic and clinical entity. It may follow the irradiation of extracranial tumors (e.g., carcinomas of the nasopharynx, scalp, paranasal sinuses), intracranial extraparenchymal tumors (pituitary adenomas), and both primary and secondary intraparenchymal tumors [1771, 680, 2134, 2855, 722, 3157, 2116, 3016, 3342, 1092, 2958, 3498, 3249, 1371, 25]. The latency period is somewhat dose dependent and varies from several months to years after exposure, with 70% of cases appearing within 3 years [1771]. An exceptional latency period has been recorded of 32 years [2368].

Radionecrosis develops in brain tissue included in the target volume of radiotherapy, which varies according to the different tumor types. In pituitary tumors, damage occurs in the temporal lobes and/or hypothalamus, seldom in the frontal lobes; with intracerebral tumors treated by whole-brain irradiation (such as malignant gliomas and metastases), the damage frequently occurs in the peritumoral tissue, far from the tumor, contralateral or bilateral, and may coexist with neoplastic tissue, both quiescent and actively growing. It has been hypothesized that structural and/or metabolic changes induced by neoplasia, mainly through edema, make peritumoral areas, which generally receive the highest doses, more prone to radiation-induced damage [391, 3016]. Generally, radionecrosis, like the other minor radiation-induced changes, prevails in the white matter, with the sparing of U fibers, corpus callosum, internal capsule, and optic pathways (Fig. 26.2). Changes may also be found in the cortex and meninges.

Histologically, the most characteristic feature of delayed radionecrosis is represented by fibrinoid necrosis of small and medium-sized vessel walls (Fig. 26.3), which frequently coexist with coagulative necrosis of the parenchyma [391, 3016]. Various associated are hyaline thickening of the vessel walls with endothelial atrophy, thrombosis, hemorrhages, telangiectasias, endothelial or adventitial hyperplasias (more rarely), and features attributable to chronic edema, such as demyelination, spongiosis, spongionecrosis, and gliosis. Endothelial cells with bizarre nuclei and bipolar cells with prominent nucleoli (probably fibroblasts altered by radiation) may be present.

The damage to the blood-brain barrier (BBB) is best seen at the ultrastructural level [1992, 2162]: Features corresponding to fibrinoid necrosis are represented by vessels with interruption of the endothelial lining and the penetration of fibrin and other blood components into the dilated subendothelial space. Vessels with an uninterrupted endothelial lining but showing surface infoldings and an increase of pinocytotic vesicles and cytoplasmic organelles are visible as well. Basal membranes appear fragmented or laminated ("onion skin" effect), and there is an increase of collagen fibers in the vessel wall.

The common clinicoradiologic picture of delayed radionecrosis is that of an expanding intracranial mass, with focal neurologic symptoms and signs: computed tomography (CT) shows a hypodense lesion which often takes up the contrast enhancement (Fig. 26.4), especially after the highest radiation doses, and is avascular on angiography study [693]. The diagnosis is difficult when the mass lesion occurs at the site of a previously irradiated tumor, as tumor recurrence and radiation necrosis

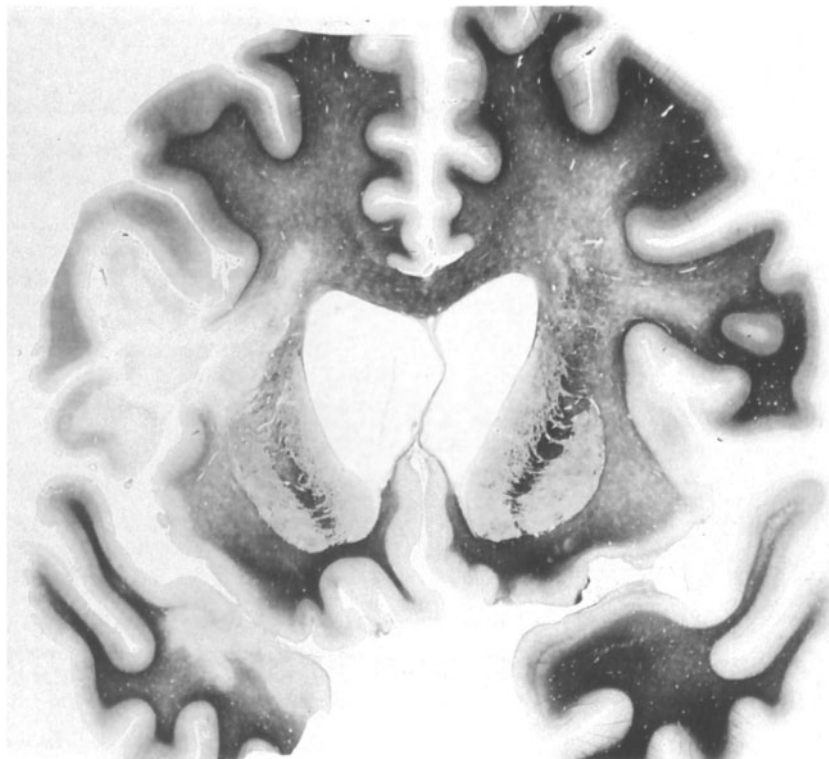


Fig. 26.2. Radiation necrosis and chronic edema in the white matter. Luxol fast blue B,  $\times 1$

with little or no persistent tumor cannot be differentiated by CT or magnetic resonance imaging (MRI) [3497]. Positron emission tomography (PET) now seems to give more valuable information [2812, 720, 760]: Utilizing as a metabolic tracer  $^{18}\text{-F}$ -2-fluoro-2-deoxyglucose, radionecrotic lesions are often hypometabolic in contrast to actively recurrent tumors, which are hypermetabolic; single photon emission CT (SPECT) with thallium-201 (a tracer of cellularity) may also be useful [366]. Biopsy remains today the only means to establish a differential diagnosis [934]. When radionecrotic lesions are multiple, the clinical picture is generally that of a progressive dementia, with diffuse hypodensity of the white matter [2264] or multiple enhancing lesions [2913] on CT scan.

The best treatment for radionecrosis presenting as a single intracranial mass is that of surgical removal [802]. Improvement has been obtained with steroids, and recently, the efficacy of anticoagulant drugs has been reported [1090].

The true incidence of pathologically proven delayed radionecrosis with little or no persistent tumor is not entirely known, due to the low percentage of patients (especially with intracerebral tumors) who are biopsied or autopsied at a distance from radiotherapy. It is very rare in extracranial tumors, its incidence ranging from 1.4% to 10.8% in pituitary adenomas [2264, 1171] and from 3% to 5% in malignant gliomas [2123, 2264, 2116, 3249], reaching 12.5% in patients surviving more than 18



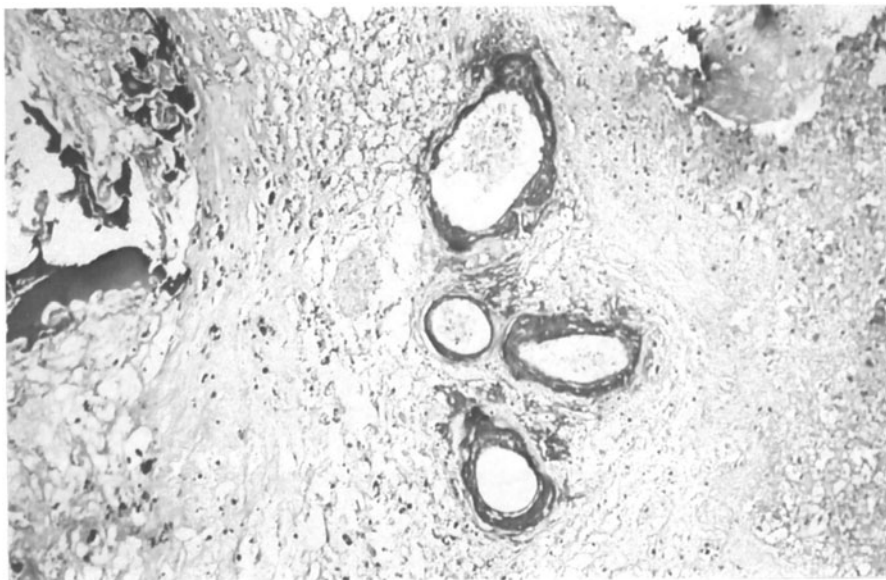


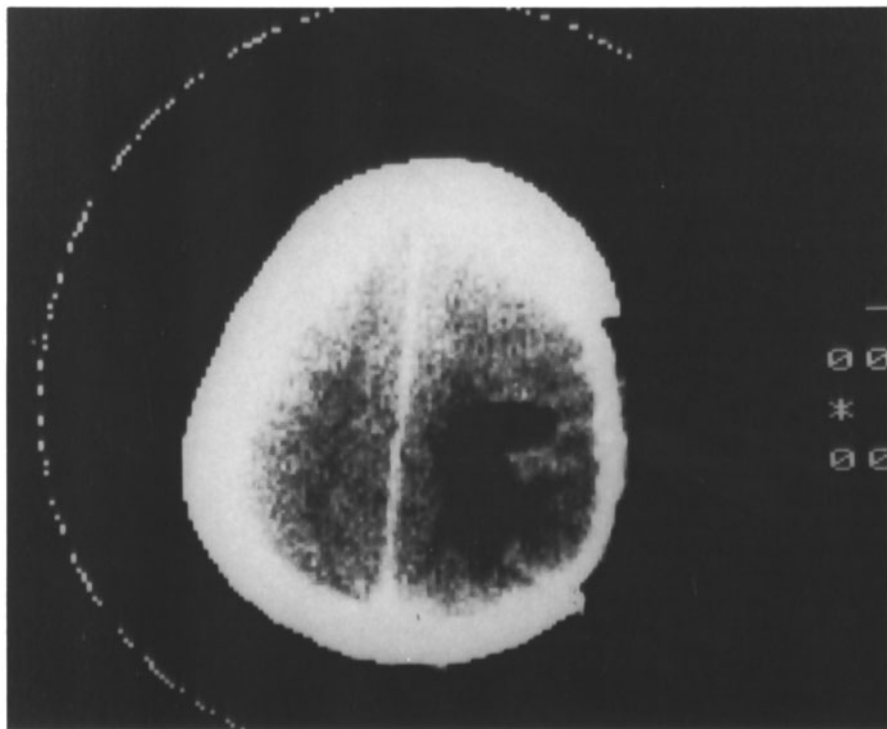
Fig. 26.3. Area of coagulative necrosis and fibrinoid degeneration of the vessel walls. H&E,  $\times 200$

months [3249]. The incidence in an autopsy series of malignant gliomas is obviously higher, reaching 10%–22% [2116, 3249].

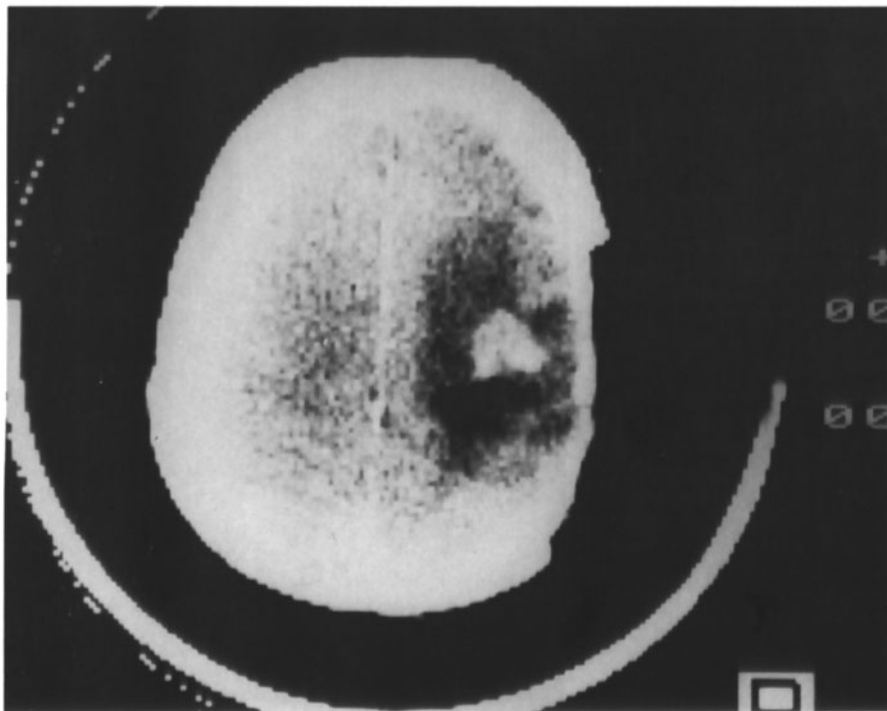
The factors influencing the risk of radionecrosis are the radiation parameters, the association with chemotherapy agents and individual characteristics. The risk increases with the increase of total radiation dose, being very rare below 5000 cGy and maximum at the highest doses (6000 cGy) [3157, 2264, 2116, 3249]. With the same total dose delivered, the risk increases using doses per fraction higher than 170–180 cGy [2116, 2915], whereas the overall treatment time is not critical. The brain volume included in the target of high doses seems to be important [2117], but no extensive studies are available. Reirradiation seems to increase the risk of late damage [763].

Hypoxic cell sensitizers do not have central neurotoxicity, whereas no data are available on the association of conventional radiotherapy with brachytherapy or hyperthermia. The use of fast neutrons instead of conventional photons increases the incidence of radionecrosis, while permitting a more efficacious tumor control [3150, 1875, 2101, 453, 791]. Chemotherapy agents such as methotrexate [331] and the nitrosoureas [3144] may increase the toxicity of radiation, especially when administered in high doses. High steroid doses during radiotherapy have a protective action [391, 3249], whereas preexisting illness such as arterial hypertension [3016], diabetes [1173], some endocrinopathies [87], and, more generally, vascular diseases [3776] may act as predisposing factors.

Fig. 26.4. a Postoperative computed tomography (CT) scan of a right parietal glioblastoma. b 18 months after radiotherapy, radionecrosis mimicking a recurrence ▷



a



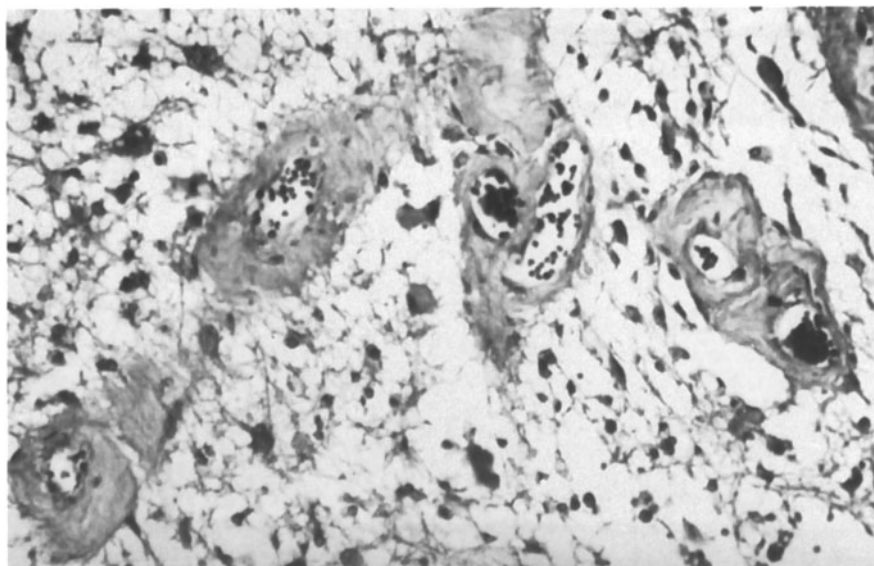
b

Independent of the picture of radionecrosis, other changes can be found in the peritumoral white matter of brains of patients autopsied at a distance from radiotherapy, [3016]: hyaline thickening of vessel walls (Fig. 26.5a), macrophagic areas (Fig. 26.5b), demyelination with loss of oligodendrocytes, spongiosis and spongionecrosis (Fig. 26.6), and gliosis. This last sometimes is so strong, with multinucleated and/or monstrous astrocytes, as to be indistinguishable from an astrocytomatous proliferation [1440]. More rarely, amyloid deposits [2090], cortical atrophy [375], and changes in the cerebellar cortex (vacuolization, loss of Purkinje cells and granules) [2904] are observed.

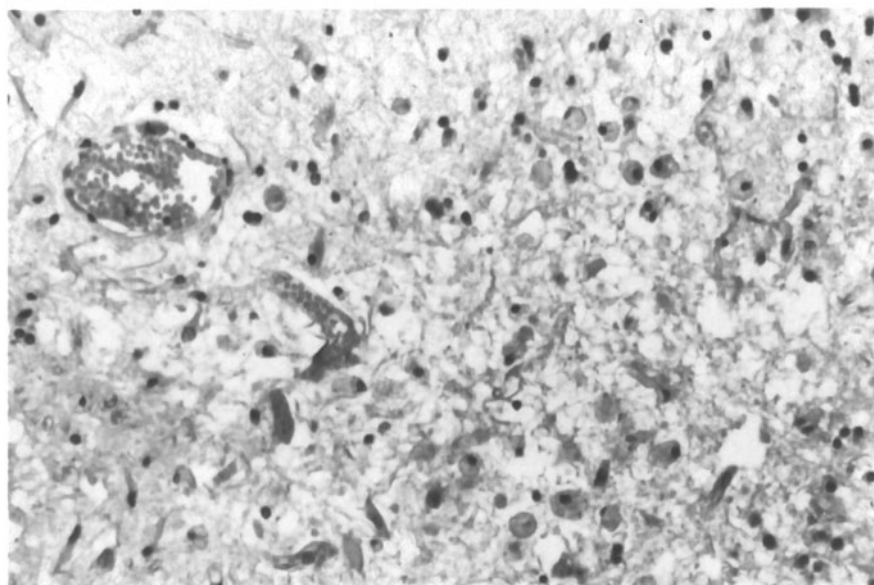
Most patients showing these changes died from tumor progression, but a few, in whom autopsy did not show tumor regrowth, suffered a slowly progressive dementia of the subcortical type. Sometimes, the clinical picture is that of a subacute leukoencephalopathy with a relatively short latency (10–24 months), which is being increasingly reported in gliomas, medulloblastomas, and metastases after treatment with unconventional radiation schedules, and with or without aggressive polychemotherapy [1898, 2529, 3241, 689]. The white matter, mainly periventricular, appears diffusely hypodense on CT and hyperintense in T2-weighted images on MRI (Fig. 26.7) [977, 3497], as seen in atherosclerotic cerebrovascular disease [3472]. Conclusions on the correlation between the pathology and neuroimaging results after treatment are not yet possible, as the number of cases adequately studied is small, and there are many discrepancies. It should be remembered that a very low incidence of cortical atrophy at autopsy in a series of patients showing CT signs of atrophy has been found [3607].

Late delayed effects include clinical sequelae which have not been pathologically substantiated. In addition to frank dementia, neuropsychologic deficits have been reported in a variable percentage of long-term survivors after whole-brain radiotherapy, both in adults [1460, 605A, 3359, 3391, 469, 2820] and in children (20% and 100%, respectively), mainly patients with medulloblastoma [1817, 547, 1508, 1093].

They consist of a reduction in intelligence quotient (IQ) with impairment of verbal, visuospatial, and memory functions [2531, 1093]. Such disturbances seem to be progressive and are greater in younger children (under 3 years of age) and in those also treated with chemotherapy (methotrexate) [780, 2802]. Visual disturbances, due to optic atrophy, fibrosis, and/or necrosis of the optic nerves, chiasm, and pathways, are in the majority described following treatment of pituitary adenomas [1242, 25]. Pituitary dysfunction is a frequent sequela of cranial irradiation. Stunted growth and failure of sexual maturation may develop in patients treated during childhood, whereas in 15%–55% of adults, signs of hypopituitarism are reported [3212A, 25]. Hypothalamic dysfunction, following whole-brain irradiation for gliomas, has been reported in 1.25% of patients, with endocrine, behavioral, and cognitive impairment [2224]: In about 50% of patients there was cortical atrophy and enlargement of the third ventricle on CT. Radiation damage to cranial nerves other than the optic one and to peripheral nerves is uncommon [1685]. Cerebral infarctions secondary to a radiation-induced damage of arterial walls (cervical and intracranial arteries) may occur [2598, 917]. It must be stressed that a number of abnormalities on CT and MRI, such as cortical atrophy, enlargement of ventricles, hypodensity, or hyperintensity on T2-weighted images of periventricular white matter, are described at a distance from the radiotherapy site in patients who are clinically normal [620, 558].



a



b

**Fig. 26.5. a** Hyaline degeneration of the vessel walls. **b** Macrophagic areas following radiotherapy. H&E,  $\times 300$

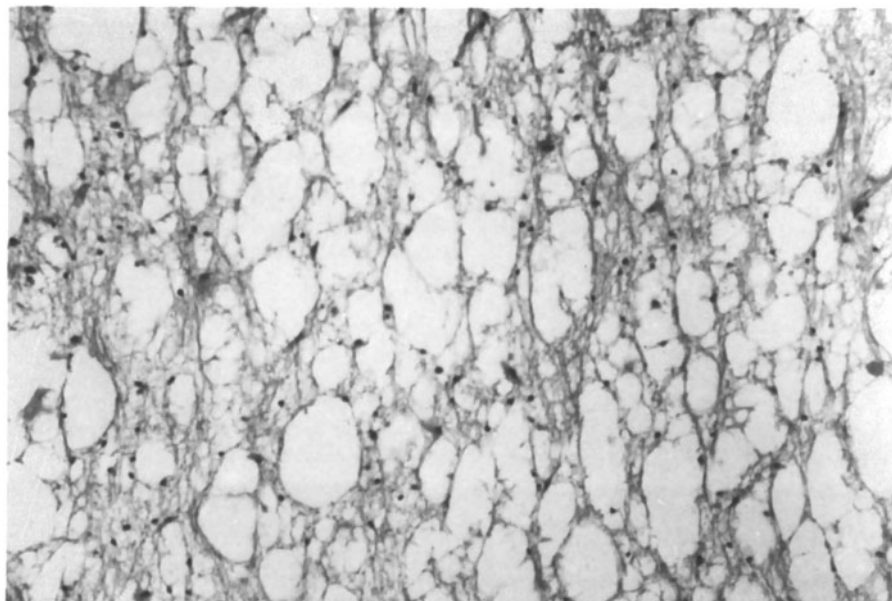


Fig. 26.6. Spongionerosis following radiotherapy. H&E,  $\times 200$

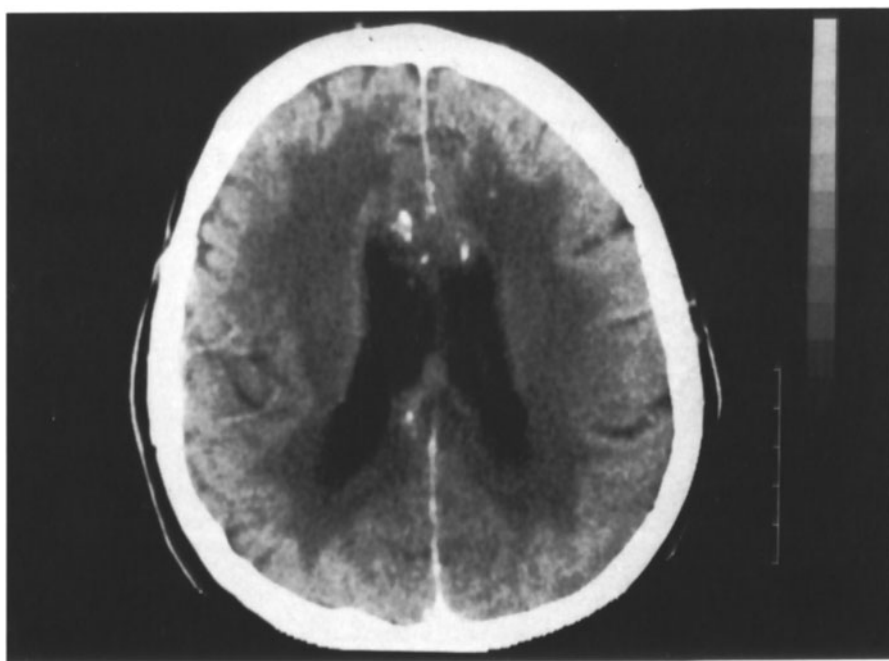


Fig. 26.7. Delayed leukoencephalopathy after radiotherapy with unconventional fractionation, computed tomography (CT) scan

### 26.3

#### Effects of Brachytherapy on the Human Brain

In the brain of patients with malignant gliomas who died after receiving  $^{125}\text{I}$  brachytherapy, three zones have been described with different expressions of the radiation damage [664]: a central necrotic zone (doses greater than 20 000 cGy) involving the tumor and, to some extent, normal white matter; a transitional zone with demyelination, vessel wall changes, and an inflammatory response (doses between 4000 and 15 000 cGy); a peripheral zone (doses less than 4000 cGy) with chronic edema and gliosis. As already observed after external radiotherapy, coagulative necrosis may involve areas receiving low doses (less than 2000 cGy) (individual susceptibility?). The location of the radiation damage depends mainly upon the tumor location: It is predominantly found in the white matter, but the cortex or nuclei of gray matter may be involved [615, 664, 1670]. The association of brachytherapy with external radiotherapy might increase the risk of damage.

### 26.4

#### Effects of External Radiotherapy on the Human Spinal Cord and/or Nerve Roots

Chronic progressive radiation myelopathy has been documented from the pathologic point of view. It follows irradiation of the cervical and thoracic spinal cord, with an incidence ranging from 0.5% [281] to 12.5% [1998] and an average value of 3% [2549]. Three quarters of patients develop myelopathy in less than 18 months, most commonly between 9 and 15 months [1850], and in a large series of cases [3092], a bimodal distribution of latency was observed with peaks occurring at 13 months (with higher doses) and 26 months (with lower doses).

Pathologically, lesions arise predominately in the white matter, especially in the deeper parts of the posterior and lateral columns [1527, 401], and in some cases may affect the entire transverse section. Based on the latency period and microscopic features, a distinction between an “early delayed” and a “late delayed” reaction has been made [1527]. The former consisted of focal areas of spongy demyelination, axonal swelling, and an absence of vascular changes, whereas the latter was similar to the delayed radionecrosis of the brain. Prominent features were, apart from coagulative necrosis, fibrinoid necrosis and hyaline changes of the vessel wall with the development of teleangiectasias. The spinal arteries and nerve roots were spared.

Clinically, the onset is insidious with paresthesias, disturbances in perceiving pain and temperature, and weakness of the legs. There is a steady progression over 6 months to involve all cord systems. Lesions tend to progress over time, coming to involve some segments of the cord not originally exposed to radiation. Most cases are fatal. Chronic progressive radiation myelopathy is a diagnosis of exclusion [2543], after ruling out other causes of myelopathy. The CSF protein level may be slightly elevated. Myelography, CT, and MRI studies frequently are normal, and only in some instances do they demonstrate swelling or mild cord atrophy.

Detailed knowledge of the radiation tolerance of the cord continues to be elusive, but some facts are well established [1127, 2191]. The risk of radiation myelopathy is

minimal after doses below 4500 cGy delivered in 180 cGy daily fractions and increases when higher total doses or a higher fraction size or a shorter treatment time is used. The tolerance depends also upon the length of treated cord. Patients who have been reirradiated are at increased risk of radiation myelopathy. Other factors, such as the association of chemotherapy agents or an individual idiosyncrasy, have been advocated in some cases.

Apart from chronic progressive myelopathy, other forms of radiation damage to the spinal cord are well known from a clinical point of view: a syndrome characterized by an acute complete paraplegia-quadruplegia due to an infarction of the spinal cord; a syndrome similar to a lower motor neuron disease; an acute transient radiation myelopathy. Well documented are the brachial plexopathy due to radiotherapy following mastectomy and the lumbosacral radiculopathy due to irradiation of the lumbosacral area [2676].

## 26.5

### Pathogenesis of Adverse Effects of Radiotherapy on the Normal Nervous Tissue

Generally, the doses utilized in clinical practice induce in the normal nervous tissue of animals only acute functional, and not morphological, changes. It has been demonstrated [1927, 706] that after doses of 200–400 cGy to the rat brain there is an increase of the BBB permeability, more evident in cortical areas, which is less intense in animals treated with dexamethasone. Modifications of the synaptic transmission [3705] and a reduction of glucose consumption [1475] have also been reported.

In the nervous tissue, the most typical effects of radiotherapy are “delayed” because the cells which are the target of the ionizing radiation (oligodendroglia and endothelium) have an extremely low turnover [2758, 1760], and time is required before a critical number of injured cells undergo mitotic death and the damage becomes clinically evident.

As for the early delayed effects, in addition to the few human pathological data, experimental studies suggest damage to the oligodendrocytes [2145, 3506]. Both in the brain and spinal cord of rats, employing high single doses (3000–4000 cGy) leads to demyelination and necrosis of the white matter, with a paucity or absence of vascular changes [1381, 3504, 1313, 3505]; the latency period (4–7 months) is inversely related to the dose and shorter than after the lower doses (1500–2000 cGy), which induce mainly vascular damage. It has, therefore, been hypothesized for the spinal cord [3505] that the radiation-induced depletion of oligodendrocytes persists with no regeneration only above a critical dose level (2000 cGy). In the brain, apart from the *in situ* depletion of oligodendroglia, the possibility of damage to the cells of the subependymal plate must also be considered. In fact, after irradiation, a reduction of both the mitotic activity [456] and the total number of cells [485] has been described, while only after the highest doses (3000–4000 cGy) was a persistent depletion obtained. When fractionated doses closer to those used in clinical practice were employed in animals, the morphologic changes in the white matter were milder [2145], and some authors reported a transitory increase of the capillary permeability [460,

2633]. Therefore, the possibility of indirect damage to the myelin and oligodendrocytes due to vasogenic edema has been suggested [708].

Three main hypotheses regarding the pathogenesis of delayed radionecrosis have been proposed, a vascular [3082, 2905, 199, 1527], a glial [1464, 3775, 401], and an immunological one [601]. The last one considers the radionecrosis as a result of a hypersensitivity reaction secondary to changes induced in the nervous tissue by the radiation and has not been further advocated. According to Russell and Rubinstein [2904], this interpretation is more in agreement with the character of the early delayed reaction described by Lampert and Davis [1852], which displayed some morphological similarities to a primary demyelinating process of an autoimmune character. On the basis of experimental data, the hypothesis of primary damage to the oligodendroglia (the basis of the glial hypothesis) seems to explain better the features of the early delayed demyelination and necrosis seen in animals after doses higher than those used in humans, whereas the damage to the endothelium (the basis of the vascular hypothesis) is almost generally recognized as “the *primum movens*” of the delayed radionecrosis both in animals and in humans [2208, 1379, 2135, 460, 3793, 1380, 896, 708]. The experimental models of delayed damage are, in fact, generally characterized by vascular lesions, and especially those induced in monkeys [2135, 460] and dogs [3793, 896] are similar to human material according to both neuropathologic and radiobiologic aspects (e.g., type of radiation treatment, latency period, CT aspects). In the rat, the late delayed damage is characterized mainly by teleangectasias in the brain, and teleangectasias associated with hemorrhages and endothelial hyperplasias in the spinal cord. Such damage develops after relatively low, single doses (1500–2000 cGy), radiobiologically equivalent to those used in humans, and after long latency periods (8–18 months) [1379, 3505, 2759, 1380]. Arterial hypertension accelerates the development of the lesions [1381]. When fractionated schedules are employed, similar to those used in humans, behavioral dysfunctions, mainly affecting memory, can be demonstrated without pathological abnormalities [1854].

It has been hypothesized that the endothelium of the brain vessels (especially capillaries) is particularly susceptible to damage from radiation-induced free radicals [3108, 478]. The radiation damages the DNA of the endothelial cells, and death occurs when the cells attempt to divide (mitotic death). The cell loss stimulates the compensatory proliferation of other endothelial cells, and when a critical number of these cells dies, a breakdown of the BBB develops, leading to an increase of permeability and penetration of blood components into the vessel wall and into the parenchyma. Vessel changes, edema with demyelination, and necrosis follow. The stimulation of the proliferative capacity of an endothelium already injured by radiation subsequent to implantation of a tumor has been demonstrated to lead to an acceleration of the development of vascular changes [3272].

It has recently been suggested for both humans [2478] and animals [706] that conventionally fractionated treatment induces alterations of the glucose metabolism in the cortex (more pronounced in associative areas) in the absence of clear pathologic changes.



## 26.6

### Effects of Chemotherapy on the Human Brain and Spinal Cord

The neurotoxic effects of cancer chemotherapy are numerous and have been extensively reviewed [375, 1521, 3144]. Here, only some types of normal nervous tissue damage related to the peculiar treatment modalities for brain tumors are described.

There are reports of central delayed neurotoxicity after high dose intravenous [392] or intra-arterial (intracarotid) administration of BCNU [1589, 2070, 1715, 2840] in patients who did not undergo cranial irradiation. The changes involved mainly the white matter, consisting of lesions similar to those of delayed radionecrosis (fibrinoid necrosis, thrombosis, hyalinization and perithelial proliferations, coagulative necrosis, edema) along with the presence, in most cases, of axonal swelling in the areas of coagulative necrosis. After the intracarotid injection of BCNU, changes were generally confined to the arterial territories infused, with a clustering of lesions in the superficial gyri and deep periventricular white matter [2840] or deep gray matter [720] in some patients. It has been suggested [392, 2840] that cumulative doses of BCNU primarily injure the blood vessels, leading to secondary tissue edema and necrosis.

In patients who had given the drug intra-arterially, other factors have been advocated to explain the neurotoxicity [929, 2070, 167, 2950]: ethanol as a diluent, an incomplete mixing of the drug and blood leading to a streaming phenomenon, and the association with radiotherapy. The clinical picture of this neurotoxicity is that of a leukoencephalopathy with more pronounced changes visible on CT and MRI scans in the territories infused and sometimes a gyral enhancement with calcifications.

A leukoencephalopathy consisting of bilateral demyelinating and necrotizing lesions involving the juxtaventricular white matter has been described following the intraventricular infusion of methotrexate [3146], especially in the presence of ventricular obstruction.

Several forms of transient or permanent neurotoxicity are not uncommon after intrathecally administered chemotherapy (methotrexate, cytarabine, thiotepe), e.g., acute meningeal and/or encephalic reactions, chronic encephalopathies, myeloradiculopathies.

## 26.7

### Effects of Treatment on Normal Nervous Tissue in Acute Lymphocytic Leukemia of Childhood

Disseminated necrotizing leukoencephalopathy (DNL) is a neurologic syndrome described mainly in children with acute lymphocytic leukemia who received prophylactic treatment of whole-brain radiotherapy (2400 cGy) before or along with the intrathecal administration of methotrexate and/or cytarabine and/or high dose methotrexate given intravenously. The incidence ranges from 2% to 15%, rising with the increase of radiation and chemotherapeutic doses [272]. In recent years after modification of the treatment modalities, such a syndrome has developed more rarely.

Pathologically, lesions were found in the cerebral white matter (with frequent involvement of the corpus callosum), midbrain, pons, and medulla. The microscopic

appearances were quite distinctive with disseminated foci of coagulative necrosis unrelated to the blood vessels, loss of myelin and oligodendroglia, severe axonal damage, and often calcifications. Fibrinoid necrosis of the vessel walls was neither constant nor extensive. As for the pathogenesis, it has been suggested [2904] that the neurotoxicity is of systemic origin, strongly potentiated by the cranial radiation and, probably, by the intrathecal administration of drugs. Clinically, the syndrome developed 4–12 months after treatments, with the typical symptoms and signs of a leukoencephalopathy, progressing in a few months to death. High levels of myelin basic protein in the CSF have been found [1019].

Mineralizing microangiopathy is a less well defined entity as pathological data are scarce and most patients are asymptomatic or present with minimal and nonspecific symptoms. In 25%–30% of patients with acute lymphocytic leukemia who are long-term survivors after prophylaxis of the CNS (radiotherapy alone or associated with methotrexate or cytarabine therapy), CT study has shown calcifications in the basal ganglia and cortex. From the pathological point of view, predominant involvement of the gray matter (cortical sulci, putamen, cerebellum) with deposition of calcium in the lumen and in the walls of small vessels and sometimes accompanied by perivascular necrosis has been observed [2689]. The pathogenesis is unknown.

In addition, after prophylactic treatment of the whole brain in children with lymphocytic leukemia, a high percentage of cognitive deficits have been reported [807, 2222].

## 26.8 Second Malignancies

For details on second malignancies, see Chap. 2.

---

## References

1. Aarli JA, Mork SJ, Myrseth E, Larsen JL (1989) Glioblastoma associated with multiple sclerosis: coincidence or induction? *Eur Neurol* 29:312–316
2. Abbott M, Namiki H (1968) Congenital ependymoma. Case report. *J Neurosurg* 28:162–165
3. Abelson HT, Kufe DW, Skarin AT, Major P, Ensminger W, Beardsley GP, Canellos GP (1981) Treatment in central nervous system tumor with methotrexate. *Cancer Treat Res* 65:137
4. Abraham J, Chandy J (1963) Meningiomas of the posterior fossa without dural attachment. A case report. *J Neurosurg* 20:177–179
5. Abramson DH, Ellsworth RM, Kitchin FD, Jung G (1984) Second non-ocular tumors in retinoblastoma survivors. Are they radiation induced? *Ophthalmology* 91:1351–1355
6. Abrikosof A (1926) Über Myome ausgehend von der quergestreiften willkürlichen Muskulatur. *Virchows Arch (Pathol Anat)* 260:215–233
7. Achilles E, Padberg B-C, Holl K, Klöppel, Schröder S (1991) Immunocytochemistry of paragangliomas – value of staining for S-100 protein and glial fibrillary acid protein in diagnosis and prognosis. *Histopathology* 18:453–458
8. Achtstätter T, Moll R, Anderson A, Kuhn C, Pitz S, Schwechheimer K, Franke WW (1986) Expression of glial filament protein (GFP) in nerve sheaths and non-neural cells re-examined using monoclonal antibodies, with special emphasis on the co-expression of GFP and cytokeratins in epithelial cells of human salivary gland and pleomorphic adenomas. *Differentiation* 31:206–227
9. Adams JH, Howatson AG (1990) Cerebral lymphomas: review of 70 cases. *J Clin Pathol* 43:544–547
10. Adams RD (1975) Certain notable clinical attributes of the histiocytic sarcomas of the central nervous system. *Acta Neuropathol (Berl) Suppl* 6:177–180
11. Adamson TE, Wiestler OD, Kleihues P, Yasargil MG (1990) Correlation of clinical and pathological features in surgically treated craniopharyngioma. *J Neurosurg* 73:12–17
12. Adegbite AB, Khan MI, Parine KWE, Tan LK (1983) The recurrence of intracranial meningiomas after surgical treatment. *J Neurosurg* 58:51–56
13. Adelman LS, Dahl D, Bignami A (1983) Chordomas stained with keratin antiserum. *J Neuropathol Exp Neurol* 42:314
14. Adey WR, Bawin SM (1982) Binding and release of brain calcium by low-level electromagnetic fields: a review. *Radiol Sci* 17:149–157
15. Aeschlimann A, Mall T, Radii E, Gratzl O (1986) Benign intra- and extracranial meningioma. *Eur Neurol* 25:125–129
16. Afra D, Müller W, Slowik F, Wilcke O, Budka H, Turoczy L (1983) Supratentorial lobar ependymomas: reports on the grading and survival periods in 80 cases, including 46 recurrences. *Acta Neurochir (Wien)* 69:243–251
17. Afra D, Müller W, Slowik F (1986) Supratentorial lobar pilocytic astrocytomas: report of 45 operated cases including 9 recurrences. *Acta Neurochir (Wien)* 81:90–93
18. Afshar F, Scholtz CL (1981) Enterogenous cyst of the fourth ventricle Case report. *J Neurosurg* 54:836–838
19. Agnoli AL, Laun A, Schönmayr R (1984) Enterogenous intraspinal cysts. *J Neurosurg* 61:834–840
20. Agosti RM, Leuthold M, Gullick WJ, Gazi-Yasargil M, Wiestler OD (1992) Expression of the epidermal growth factor receptor in astrocytic tumours is specifically associated with glioblastoma multiforme. *Virchows Arch Pathol Anat* 420:321–325

21. Agranovich AL, Ang L-C, Fryer CJH (1993) Central neurocytoma: Report of 2 cases and literature review. *J Neurooncol* 16:47-53
22. Aguzzi A, Kleihues P, Heckl K, Wiestler OD (1991) Cell type-specific tumor induction in neural transplants by retrovirus-mediated oncogene transfer. *Oncogene* 6:113-118
23. Ahlbom A, Norell S, Rodwall Y (1986) Dentists, dental nurses and brain tumors. *Br Med J* 292:662-665
24. Akesson HO, Axelsson R, Samnelsson B (1983) Neurofibromatosis in monozygotic twins: a case report. *Acta Genet Med Gemell* 32:245-249
25. Al-Mefty O, Kersh JE, Routh A, Smith RR (1990) The long-term side effects of radiation therapy for benign brain tumors in adults. *J Neurosurg* 73:502-512
26. Albert DM (1982) Tumors of the retina. In: Garner A, Klintworth GK (eds) *Pathobiology of ocular diseases*, part A. Dekker, New York, pp 705-726
27. Albrecht P (1904) Ueber Hamartome. *Verh Dtsch Ges Pathol* 7:153-157
28. Albrecht S, Connelly JH, Bruner JM (1993) Distribution of p53 protein expression in gliosarcomas: an immunohistochemical study. *Acta Neuropathol (Berl)* 85:222-226
29. Albrecht S, von Deimling A, Pietsch T, Giangaspero F, Brandner S, Kleihues P, Wiestler OD (1994) Microsatellite analysis of loss of heterozygosity on chromosomes 9q, 11p and 17p in medulloblastomas. *J Neuropathol Appl Neurobiol* 20:74-81
30. Albrechtsen R, Klee JG, Moller JE (1972) Primary intracranial germ cell tumors including five cases of endodermal sinus tumor. *Acta Pathol Microbiol Scand [Suppl]* 233:32-38
31. Albright AL, Guthkelch AN, Packer RJ, Price RA, Rorke LB (1986) Prognostic factors in pediatric brain-stem gliomas. *J Neurosurg* 65:751-755
32. Alderson LM, Castleberg RL, Harsh IV GR, Louis DN, Henson JW (1995) Human gliomas with Wild-Type p53 express bcl-2<sup>l</sup>. *Cancer Res* 55:999-1001
33. Alexander P (1969) Comparison of the mode of action by which some alkylating agents and ionizing radiations kill mammalian cells. *Ann NY Acad Sci* 163:652-675
34. Alexander V, Leffingwell SS, Lloyd JW (1982) Investigation of an apparent increased prevalence of brain tumors in a U.S. petrochemical plant. *Ann NY Acad Sci* 381:97-107
35. Ali IV, Hynes RO (1978) Effects of LETs glycoprotein on cell motility. *Cell* 14:439-446
36. Ali-Osman F (1989) Glutathione and glutathione-S-transferase in human brain tumor resistance to chloroethylnitrosoureas (CENUs). *J Neurooncol* 7 [Suppl] 3
37. Ali-Osman F, Stein DE, Renwick A (1990) Glutathione content and glutathione-S-transferase expression in 1,3-bis(2-chloroethyl)-1-nitrosourea-resistant human malignant astrocytoma cell lines. *Cancer Res* 50:6976-6980
38. Allegranza A, Migliavacca F, Mariani C (1980) Xantoastrocitoma pleomorfo cerebro-meningeo. *Istocitopatologia* 2:137-141
39. Allegranza A, Mariani C, Giardini R, Brambilla MC, Boeri R (1984) Primary malignant lymphomas of the central nervous system: a histological and immunohistological study of 12 cases. *Histopathology* 8:781-791
40. Allen JC, Bloom J, Ertel I, Evans A, Hammond D, Jones H, Levin V, Jenkin D, Spoto R, Wara W (1985) Brain tumors in children: current cooperative and institutional chemotherapy trials in newly diagnosed and recurrent disease. *Semin Oncol* 13: 110-122
41. Allen N (1957) Cytochrome oxidase in human brain tumours. *J Neurochem* 2:37-44
42. Allen RA, Latta H, Straatsma BR (1962) Retinoblastoma. *Invest Ophthalmol* 1:728-735
43. Alles JU, Bosslet K, Schachennmayr W (1986) Hemangioblastoma of the cerebellum - an immunocytochemical study. *Clin Neuropathol* 5:238-241
44. Allhoff EP, Proppe KH, Chapman CM (1983) Evaluation of prostatic-specific acid phosphatase and prostate-specific antigen. *J Urol* 129:316-319
45. Aloisi F, Agresti C, D'Urso D, Levi G (1988) Differentiation of bipotential glial precursor into oligodendrocytes is promoted by interaction with type-1 astrocytes in cerebellar cultures. *Proc Natl Acad Sci USA* 85:6167-6171
46. Alper T (1971) Cell death and its modification: the role of primary lesions in membranes and DNA. In: *Biophysical aspects of radiation quality*. IAEA, Vienna, p 171
47. Alpers C, Davies R, Wilson C (1982) Persistence and late malignant transformation of childhood cerebellar astrocytoma: case report. *J Neurosurg* 57:548-551
48. Alsopp G, Gamble HJ (1979) An electron microscopic study of the developing capillaries in human fetal brain and muscle. *J Anat* 128:155-168

49. Alter M (1975) Statistical aspects of spinal cord tumours. In: Vinken PJ, Bruyn GW (eds) *Handbook of clinical neurology*, vol 19. North-Holland, Amsterdam, pp 1–22
50. Altinörs N, Senveli E, Erdogan A, Arda N, Pak I (1984) Craniopharyngioma of the cerebello-pontine angle. Case report. *J Neurosurg* 60:842–844
51. Altman J, Bayer SA (1978) Development of the diencephalon in the rat III. Ontogeny of the specialized ventricular linings of the hypothalamic third ventricle. *J Comp Neurol* 182:995–1016
52. Alvarez-Garijo JA, Froufè A, Taboada D, Vila M (1981) Successful surgical treatment of an odontogenic ossified craniopharyngioma. Case report. *J Neurosurg* 55:832–835
53. Alvarez-Garijo JA, Albiach VJ, Vila M, Mulas F, Eoquembre V (1983) Precocious puberty and hypothalamic hamartoma with total recovery after surgical treatment. Case report. *J Neurosurg* 58:583–585
54. Alvord EC (1975) Why do gliomas not metastatize? *Arch Neurol* 33:73–75
55. Alvord EC, Lofton S (1988) Gliomas of the optic nerve or chiasm: outcome by patient's age, tumor site, and treatment. *J Neurosurg* 68:85–98
56. Amacher AL (1980) Craniopharyngioma: the controversy regarding radiotherapy. *Childs Brain* 6:57–64
57. Amacher AL, Torres QV, Rittenhouse S (1986) Congenital medulloblastoma: an inquiry into origins. *Childs Nerv Syst* 2:262–265
58. Ambler M (1977) Striated muscle cells in the leptomeninges in cerebral dysplasia. *Acta Neuropathol (Berl)* 40:269–271
59. Ambler M, Pogacar S, Sidman R (1969) Lhermitte-Duclos disease (granule cell hypertrophy of the cerebellum). Pathological analysis of the first familial cases. *J Neuropathol Exp Neurol* 28:622–647
60. Ammirati M, Galicich JH, Arbit E, Liao Y (1987) Reoperation in the treatment of recurrent intracranial malignant gliomas. *Neurosurgery* 21:607–614
61. Anderson FM, Adelstein LJ (1942) Gangliocytoma. *Arch Surg* 45:129–138
62. Anderson HC (1969) Vesicles associated with calcification in the matrix of epiphseal cartilage. *J Cell Biol* 41:59–72
63. Anderson M, Hughes B, Jefferson W, Smith WT, Waterhouse JAH (1980) Gliomatous transformation and demyelinating diseases. *Brain* 103:603–622
64. Anderson MS (1966) Mixopapillary ependymomas presenting in the soft tissue over the sacrococcygeal region. *Cancer* 19:585–590
65. Andersson A-M, Moran N, Gaardsvoll H, Linnemann D, Bjerkvig R, Laerum OD, Back E (1991) Characterization of NCAM expression and function in BT4C and BT4Cn glioma cells. *Int J Cancer* 47:124–129
66. Andrioli GC, Scanarini M, Iob I (1979) Intrinsic haematopoietic activity of cerebellar haemangioblastomas. Ultrastructural study of three cases. *Neurochirurgia (Stuttg)* 22:24–28
67. Andrioli GC, Zuccarello M, Scanarini A, d'Avilla D (1981) Concurrent primary intracranial tumours of different histogenesis. *Acta Neuropathol (Berl) Suppl* 7:111–115
68. Ang KK, Van Der Kogel AJ, Van Dam J, Van Der Schueren E (1984) The kinetics of repair of sublethal damage in the rat cervical spinal cord during fractionated irradiations. *Radiother Oncol* 1:247–253
69. Ang LC, Plewes M, Tan L, Begley H, Agranovic A, Shul D (1994). Proliferating cell nuclear antigen expression in the survival of astrocytoma patients. *Can J Neurol Sci* 21:306–310
70. Annegers JF, Coulam CB, Abboud CF, Laws ER Jr, Kurland LT (1978) Pituitary adenoma in Olmsted County, Minnesota, 1935–1977: a report of an increasing incidence of diagnosis in women of childbearing age. *Mayo Clin Proc* 53:641–643
71. Annegers JF, Laws ER, Kurland LT, Grabow JD (1979) Head trauma and subsequent brain tumors. *Neurosurgery* 4:203–205
72. Annegers JF, Schoenberg BS, Okazaki H, Kurland LT (1981) Epidemiologic study of primary intracranial neoplasms. *Arch Neurol* 38:217–219
73. Antanitus DS, Choi BH, Lapham LW (1976) The demonstration of glial fibrillary acidic protein in the cerebrum of the human fetus by indirect immunofluorescence. *Brain Res* 103:613–616
74. Antinheimo J, Haapasalo H, Seppälä M, Sainio M, Carpen O, Jääskeläinen J (1995) Proliferative potential of sporadic and neurofibromatosis 2-associated Schwannomas as studied by MIB.1 (Ki-67) and PCNA labeling. *J Neuropathol Exp Neurol* 54:776–782

75. Antoni N (1920) Über Rückenmarkstumoren und Neurofibrome. Bergmann, Wiesbaden
76. Antoniades HN, Galanopoulos T, Neville-Golden J, Maxwell M (1992) Expression of insulin-like growth factors I and II and their receptor mRNAs in primary human astrocytomas and meningiomas; in vivo studies using in situ hybridization and immunohistochemistry. *Int J Cancer* 50:215–222
77. Anzil AP (1970) Glioblastoma multiforme with extracranial metastases in the absence of previous craniotomy: case report. *J Neurosurg* 33:88–94
78. Apodaca G, Rutka JT, Bouhana K, Berens ME, Giblin JR, Rosenblum ML, McKerrow JH, Banda MJ (1990) Expression of metalloproteinases and metalloproteinase inhibitors by fetal astrocytes and glioma cells. *Cancer Res* 50:2322–2329
79. Apuzzo MLJ, Mitchell MS (1981) Immunological aspects of intrinsic glial tumors. *J Neurosurg* 55:1–18
80. Apuzzo MLJ, Chandrasoma PT, Cohen D, Zee C-S, Zelman V (1987) Computed imaging stereotaxy: experience and perspective related to 500 procedures applied to brain masses. *Neurosurgery* 20:930–937
81. Araki C, Matsumoto S (1969) Statistical reevaluation of pinealoma and related tumors in Japan. *J Neurosurg* 30:146–149
82. Arbit E, Wronski M, Burt M, Galicich JH (1995) The treatment of patients with recurrent brain metastases: a retrospective analysis of 109 patients with nonsmall cell lung cancer. *Cancer* 76:765–7773
83. Arem R, Zoghbi W, Chan L (1985) Amenorrhea-galactorrhea and craniopharyngioma. *Surg Neurol* 20:109–112
84. Arends MJ, McGregor AH, Wyllie AH (1994) Apoptosis is inversely related to necrosis and determines net growth in tumours bearing constitutively expressed myc, ras, and HPV oncogenes. *Am J Pathol* 144:1045–1057
85. Arendt A, Senitz D (1972) Histologische Kriterien zur biologischen Wertigkeit beim Ependyom. *Arch Geschwulstforsch* 40:44–50
86. Aricò M, Raiteri E, Bossi G, Giordana MT, Corbella F, Locatelli D, Pezzotta S (1994) Choroid plexus carcinoma: report of one case with favourable response to treatment. *Med Pediatr Oncol* 22:274–278
87. Aristizabal SA, Boone MLM, Laguna JF (1979) Endocrine factors influencing radiation injury to central nervous tissue. *Int J Radiat Oncol Biol Phys* 5:349–353
88. Arita N, Ushio Y, Hayakawa T, Watanabe M, Maeda Y, Kanai N, Mogami H (1979) Primary intracranial germ cell tumor. *No Shinkei Geka* 7:465–474
89. Arita N, Ushio Y, Hayakawa T et al (1984) Meningeal giomatosis: a study of 10 cases. *No Shinkei Geka* 36:775–780
90. Ariza A, Fernandes LA, Inagami T, Kim JH, Manuelidis EE (1988) Renin in glioblastoma multiforme and its role in neovascularization. *Am J Clin Pathol* 90:437–441
91. Armstrong DD (1993) The neuropathology of temporal lobe epilepsy. *J Neuropathol Exp Neurol* 52:433–443
92. Arnetoli G, Nencioni L, Sottini M, Ammanati F (1983) Simultaneous meningioma and glioma. Difficulties of neuroradiological diagnosis. Report of a case. *Ital J Neurol Sci* 4:481–483
93. Arnold H, Zimmerman HM (1943) Experimental brain tumors. III Tumors produced by dibenzanthracene. *Cancer Res* 3:682–685
94. Arnstein LH, Boldrey E, Naffziger HC (1951) A case report and survey of brain tumors during the neonatal period. *J Neurosurg* 8:315–319
95. Aronson HA, Otis RD (1962) Intracranial chondroma involving the cerebellopontine angle. Report of a case. *J Neurosurg* 19:529–531
96. Aronson SM, Aronson BE (1965) Central nervous system in diabetes mellitus: lowered frequency of certain intracranial neoplasms. *Arch Neurol* 12:390–398
97. Arseni C, Cinrea AV (1981) Statistical survey of 276 cases of medulloblastoma (1935–1978). *Acta Neurochir (Wien)* 57:159–162
98. Arthur K (1977) Radiotherapy in chemodectomas of the glomus jugulare. *Clin Radiol* 28:415–417
99. Artico M, Bardella L, Ciappetta P, Rato A (1989) Surgical treatment of subependymomas of central nervous system. *Acta Neurochir (Wien)* 98:25–31

100. Artigas J, Cervos-Navarro J, Iglesias JR, Ebhardt G (1985) Gliomatosis cerebri: clinical and histological findings. *Clin Neuropathol* 4:135–148
101. Askanazy H (1938) Les tumeurs perlées du nevraxe. *Encephale* 1:209–238
102. Askenasy H, Behmoaram (1960) Subarchnoid hemorrhage in meningioma of the lateral ventricle. *Neurology* 10:484–489
103. Aström KE, Webster Hde F, Arnazon BG (1968) The initial lesions in experimental allergic neuritis. *J Exp Med* 128:469–496
104. Aubert L, Arroyo H, Dumas G, Tripier MF (1968) Un cas d'association entre sclérose en plaques et glioblastome cérébral. *Rev Neurol* 119:374–376
105. Auer RN, Becker LE (1983) Cerebral medulloepithelioma with bone, cartilage, and striated muscle. Light microscopic and immunohistochemical study. *J Neuropathol Exp Neurol* 42:256–261
106. Auer R, Rice G, Hinton G, Annacher A, Gilbert J (1981) Cerebellar astrocytoma with benign histology and malignant clinical course: case report. *J Neurosurg* 54:128–132
107. Augenstein HM, Sze G, Becker R (1991) Imaging of spinal meningiomas. In: Al-Mefty O (ed) *Meningiomas*. Raven, New York, pp 603–614
108. Auperin I, Mikol J, Oksenhendler E, Thiebaut J, Brunet M, Dupont B, Morinet F (1994) Primary central nervous system malignant non-Hodgkin's lymphomas from HIV-infected and non-infected patients. Expression of cellular surface proteins and Epstein-Barr viral markers. *Neuropathol Appl Neurobiol* 20:243–252
109. Ausman JJ, Shapiro WR, Rall D (1970) Studies on the chemotherapy of experimental brain tumors: development of an experimental model. *Cancer Res* 30:2394–2400
110. Austin EJ, Alvord EC Jr (1988) Recurrences of cerebellar astrocytomas: a violation of Collin's law. *J Neurosurg* 68:41–47
111. Austin SG, Schnatter AR (1983) A case-control study of chemical exposures and brain tumors in petrochemical workers. *J Occup Med* 25:313–320
112. Austin-Seymour M, Munzenrider J, Goitien M, Verhey L, Uric M, Gentry R, Birnbaum S, Ruotolo D, McManus P, Skates S, Ojemann RG, Rosemberg A, Schiller A, Koehler A, Suit HD (1989) Fractionated proton radiation therapy of chordoma and low-grade chondrosarcoma of the base of the skull. *J Neurosurg* 70:13–17
113. Averbach P (1978) Mixed intracranial sarcomas: rare forms and a new association with previous radiation therapy. *Ann Neurol* 4:229–233
114. Awad I, Bay JW, Rogers L (1986) Leptomeningeal metastasis from supratentorial malignant gliomas. *Neurosurgery* 19:247–251
115. Axelrod J (1974) The pineal gland: a neurochemical transducer. Chemical signals from nerves regulate synthesis of melatonin and convey information about internal clocks. *Science* 184:1341–1348
116. Aydin F, Ghatak NR, Salvant J, Muizelaar P (1993) Desmoplastic cerebral astrocytoma of infancy. A case report with immunohistochemical, ultrastructural and proliferation studies. *Acta Neuropathol (Berl)* 86:666–670
117. Azzarelli B, Rekate HL, Roessmann U (1977) Subependymoma: a case report with ultrastructural study. *Acta Neuropathol (Berl)* 40:279–282
118. Azzarelli B, Richards DE, Anton, Roessmann U (1977) Central neuroblastoma: electron microscopic observations and catecholamine determinations. *J Neuropathol Exp Neurol* 36:384–397
119. Azzarelli B, Luerssen TG, Wolfe TM (1991) Intramedullary secretory gangliocytoma. *Acta Neuropathol (Berl)* 82:402–407
120. Backlund EO, Axelsson B, Bergstrand CG, Eriksson AL, Noren G, Ribbesjo E, Rahn T, Schnell PO, Tallstedt L, Saaf M, Thoren M (1989) Treatment of craniopharyngiomas – the stereotactic approach in a ten to twenty three years perspective. I. Surgical, radiological and ophthalmological aspects. *Acta Neurochir (Wien)* 99:11–19
121. Bader JL, Meadows AT, Zimmerman LE, Rorke LB, Voute PA, Champion LAA, Miller RW (1982) Bilateral retinoblastoma with ectopic intracranial retinoblastoma: trilateral retinoblastoma. *Cancer Gen Cytogen* 5:203–213
122. Bader YL, Meadows AT, Zimmerman LE, Rorke LB, Voute PA, Champion LA, Miller RW (1982) Bilateral retinoblastoma with ectopic intracranial retinoblastoma: trilateral retinoblastoma. *Cancer Genet Cytogenet* 5:203–213

123. Badiali M, Pession A, Basso G, Andreini L, Rigobello L, Galassi E, Giangaspero F (1991) N-myc and c-myc oncogenes amplification in medulloblastomas. Evidence of particularly aggressive behavior of a tumor with c-myc amplification. *Tumori* 77:118-121
124. Bahemuka M (1983) Worldwide incidence of primary nervous system neoplasms. Geographical, racial and sex differences, 1960-1977. *Brain* 111:737-755
125. Bahemuka M, Massey W E, Schoenberg BS (1988) International mortality from primary nervous system neoplasms: distribution and trends. *Int J Epidemiol* 17:33-38
126. Bailey P (1924) A study of tumors arising from ependymal cells. *Arch Neurol Psychiat* 11:1-27
127. Bailey P (1932) Cellular types in primary tumors of the brain. In: Penfield W (ed) *Cytology and cellular pathology of the nervous system*. Hoeber, New York, pp 905-951
128. Bailey P (1933) Intracranial tumors. Thomas, Springfield
129. Bailey P, Bucy PC (1929) Oligodendrogliomas of the brain. *J Pathol Bacteriol* 32:735-751
130. Bailey P, Bucy PC (1930) Astroblastomas of the brain. *Acta Psychiatr Neurol Scand* 5:439-461
131. Bailey P, Bucy PC (1931) The origin and nature of meningeal tumors. *Am J Cancer* 15:15-54
132. Bailey P, Cushing H (1925) Medulloblastoma cerebelli; a common type of midcerebellar glioma of childhood. *Arch Neurol Psych* 14:192-223
133. Bailey P, Cushing H (1926) A classification of the tumors of the glioma group on a histogenetic basis with a correlation study of prognosis. Lippincott, Philadelphia
134. Bailey P, Cushing H (1930) Die Gewebsverchiedenheit der Gliome und ihre Bedeutung für die Prognose. Fischer, Jena
135. Baird A, Mormede P, Bohlen P (1985) Immunoreactive fibroblast growth factor in cells of peritoneal exudate suggests its identity with macrophage-derived growth factor. *Biochem Biophys Res Commun* 126:358-364
136. Baird M, Gallagher PI (1989) Recurrent intracranial and spinal meningiomas: clinical and histological features. *Clin Neuropathol* 8:41-44
137. Baker DL, Molenaar WM, Trojanowski JQ, Evans AE, Ross AH, Rorke LB, Packer RJ, Lee VM-Y, Pleasure D (1991) Nerve growth factor receptor expression in peripheral and central neuroectodermal tumors, other pediatric brain tumors. *Am J Pathol* 139:115-122
138. Balagura S, Shulman K, Sobel EH (1979) Precocious puberty of cerebral origin. *Surg Neurol* 11:315-326
139. Baldini M, Mosca L, Princi L (1980) The empty sella syndrome secondary to Rathke's cleft cyst. *Acta Neurochir (Wien)* 53:69-78
140. Bale PM, Parsons RE, Stevens MM (1983) Diagnosis and behavior of juvenile rhabdomyosarcoma. *Hum Pathol* 14:596-611
141. Balmaceda C, Gaynor JJ, Sun M, Gluck JT, DeAngelis LM (1995) Leptomeningeal tumor in primary central nervous system lymphoma: recognition, significance and implications. *Ann Neurol* 38:202-209
142. Balthasar K (1964) Intramedullary neuromas of the spinal cord. *J Neuropathol Exp Neurol* 23:201
143. Bamborschke S, Ebhardt G, Szelies-Stok B, Drecsbach HA, Heiss WD (1985) Review and case report: primary melanoblastosis of the leptomeninges. *Clin Neuropathol* 4:47-55
144. Banda MJ, Knighton DR, Hunt TK, Werb Z (1982) Isolation of a nonmitogenic angiogenesis factors from wound fluid. *Proc Natl Acad Sci (USA)* 79:7773-7777
145. Banerjee RHW, Sharma BS, Kak VK, Ghatak NR (1989) Gliosarcoma with cartilage formation. *Cancer* 63:518-523
146. Banna M (1973) Craniopharyngiomas in adults. *Surg Neurol* 1:202-204
147. Bar T (1983) Patterns of vascularization in the developing cerebral cortex. In: *Development of vascular system*. Ciba Foundation Symposium 100. Pitman, London, pp 20-36
148. Barbareschi M, Juzzolino P, Pennella A, Allegranza A, Arrigoni G, Dalla Palma P, Doglioni C (1992) p53 protein expression in central nervous system neoplasms. *J Clin Pathol* 45:560-565
149. Bargmann CI, Hung M-C, Weinberg RA (1986) Multiple independent activations of the neu oncogene by a point mutation altering the transmembrane domain of p185. *Cell* 45:649-657
150. Barker D, Wright E, Nguyen K, Cannon L, Fain P, Goldgar D, Bishop DT, Carey J, Baty B, Kivlin J, Willard H, Wayne JS, Greig G, Leinwand L, Nakamura Y, O'Connell P, Leppert M, Lalouel J-M, White R, Skolnik M (1987) Gene for von Recklinghausen neurofibromatosis is in the pericentromeric region of chromosome 17. *Science* 236:1100-1102



151. Barker DJP, Weller RO, Garfield JS (1976) Epidemiology of primary tumours of the brain and spinal cord: a regional survey of southern England. *J Neurol Neurosurg Psychiatry* 39:290–296
152. Barker M, Deen DF, Baker DG (1979) BCNU and X-ray therapy of intracerebral 9L rat tumours. *Int J Radiat Oncol Biol Phys* 5:1581–1583
153. Barnard RO (1968) The development of malignancy in oligodendrogliomas. *J Pathol Bacteriol* 96:113–123
154. Barnard RO, Geddes JF (1987) The incidence of multifocal cerebral gliomas. A histologic study of large hemisphere sections. *Cancer* 60:1519–1531
155. Barnard RO, Jellinek EH (1967) Multiple sclerosis with amyotrophy complicated by oligodendroglioma. History of recurrent herpes zoster. *J Neurol Sci* 5:441–455
156. Barnard RO, Panbakian H (1980) Astrocytic differentiation in medulloblastoma. *J Neurol Neurosurg Psychiatry* 43:1041–1044
157. Barnard RO, Bradford R, Scott T, Thomas DGT (1986) Gliomyosarcoma. Report of a case of rhabdomyosarcoma arising in a malignant glioma. *Acta Neuropathol (Berl)* 69:23–27
158. Barone BM, Eldvidge AR (1970) Ependymomas. A clinical survey. *J Neurosurg* 33:428–438
159. Barranco SC, Romsdahl MM, Humphrey RM (1971) The radiation response of human malignant melanoma cells grown in vitro. *Cancer Res* 31:380–383
160. Barranco SC, Ford PJ, Townsend CM Jr (1989) Heterogeneous survival and cell kinetics responses of human astrocytoma clones to  $\alpha$ -difluoromethylornithine in vitro. *Investigat New Drugs* 7:155–161
161. Barraquer-Ferré L, Tolosa E, Barraquer-Bordas L, Duran F (1950) Intradural lipoma of the spinal cord. *Acta Psychiatr Neurol Scand* 25:7–17
162. Barret CP, Guth L, Donati EJ, Krikorian JG (1981) Astroglial reaction in the grey matter of lumbar segments after mid-thoracic transection of the adult rat spinal cord. *Exp Neurol* 73:365–377
163. Bartal AD, Djaldetti MM, Mandell EM, Lerner HA (1973) Dumb bell neurinoma of the hypoglossal nerve. *J Neurol Neurosurg Psychiatry* 36:592–595
164. Bartlett PF (1982) Pluripotential hemopoietic stem cells in adult mouse brain. *Proc Natl Acad Sci USA* 79:2717–2725
165. Bartlett PF, Noble MD, Pruss RM, Raff MC, Rattray S, Williams LA (1981) Rat neural antigen-2 (Ran-2): a cell surface antigen on astrocytes, ependymal cells, Müller cells and leptomeninges defined by a monoclonal antibody. *Brain Res* 204:339–351
166. Bartowski HM (1984) Peritumoral edema. *Prog Exp Tumor Res* 27:179–190
167. Bashir R, Hochberg FH, Linggood RM, Hottelmann K (1988) Pre-irradiation internal carotid artery BCNU in the treatment of glioblastoma multiforme. *J Neurosurg* 68:917–919
168. Bashir R, Freedman A, Harris N, Bain K, Nadler L, Hochberg F (1989) Immunophenotypic profile of CNS lymphoma: a review of eighteen cases. *J Neurooncol* 7:249–254
169. Bashir R, Luka J, Cheloha K, Chamberlain M, Hochberg F (1993) Expression of Epstein-Barr virus proteins in primary CNS lymphoma in AIDS patients. *Neurology* 43:2358–2362
170. Batra SK, McLendon RE, Koo JS, Castelino-Prabhu S, Fuchs HE, Krisner JP, Friedman HS, Bigner DD, Bigner FH (1995) Prognostic implications of chromosome 17p deletions in human medulloblastomas. *J Neurooncol* 24:39–45
171. Battista AF, Bloom W, Loffman H, Feigin I (1961) Autotransplantation of anaplastic astrocytomas into the subcutaneous tissue of man. *Neurology* 11:977–981
172. Batzdorf V, Malamud N (1963) The problem of multicentric gliomas. *J Neurosurg* 20:122–136
173. Bauchhenss G, Schürmann K (1962) Die intracraniellen Epidermoide. Ein Beitrag zur ihrer Artdiagnose und operative Behandlung. *Zbl Neurochir* 22:129–161
174. Baumann CHM, Bucy PC (1956) Paratriginial epidermoid tumours. *J Neurosurg* 13:455–468
175. Baumgartner JE, Rachlin JB, Beckstead JH, Meeker TC, Levy RM, Wara WM, Rosenblum ML (1990) Primary central nervous system lymphomas: natural history and response to radiation therapy in 55 patients with acquired immunodeficiency syndrome. *J Neurosurg* 73:206–211
176. Bayoumi ML (1948) Rathke's cleft and its cysts. *Edinburgh Med J* 55:745–749
177. Beatty RA (1972) Malignant melanoma of the choroid plexus epithelium: case report. *J Neurosurg* 36:344–347
178. Beaugié JM, Mann CV, Butler ECB (1969) Sacrococcygeal chordoma. *Br J Surg* 56:586–588
179. Beck H (1883) Über ein Teratom der Hypophysis Cerebri. *Z Heilkunde* 4:393–401

180. Becker DH, Wilson CB (1981) Symptomatic parasellar granular cell tumors. *Neurosurgery* 8:173–180
181. Becker DP, Benyo R, Roessmann U (1967) Glial origin of monstrocellular tumor. Case report of prolonged survival. *J Neurosurg* 26:72–77
182. Becker I, Roggendorf W (1989) Immunohistological investigation of mononuclear cell infiltrates in meningiomas. *Acta Neuropathol (Berl)* 79:211–216
183. Becker LE (1989) Primitive neuroectodermal tumors: views on a working classification. In: Fields WS (ed) *Primary brain tumors. A review of histologic classifications*. Springer, Berlin Heidelberg New York, pp 58–69
184. Becker LE, Hinton D (1983) Primitive neuroectodermal tumors of the central nervous system. *Hum Pathol* 14:538–550
185. Becker RL, Becker AD, Sobel DF (1995) Adult medulloblastoma: review of 13 cases with emphasis on MRI. *Neuroradiology* 37:104–108
186. Begg CE, Garrett R (1954) Hemangiopericytoma occurring in the meninges. *Cancer* 7:602–606
187. Beitz JG, Kim I, Calabresi P, Frackelton AR Jr (1991) Human microvascular endothelial cells express receptors for platelet-derived growth factor. *Proc Natl Acad Sci USA* 88:2021–2025
188. Belamaric J, Cham AS (1969) Medulloblastoma in newborn sisters. Report of two cases. *J Neurosurg* 30:76–79
189. Bell DA, Woodruff JM, Scully RE (1984) Ependymoma of the broad ligament. A report of two cases. *Am J Surg Pathol* 8:203–209
190. Bello MJ, de Campos JM, Kusak ME, Vaquero J, Sarasa JL, Pestana A, Rey JA (1994) Molecular analysis of genomic abnormalities in human gliomas. *Cancer Genet Cytogenet* 73:122–129
191. Bellon G, Cautel T, Cam Y, Plerot M, Poulin G, Pytlinska M, Bernard MH (1985) Immunohistochemical localization of macromolecules of the basement membrane and extracellular matrix of human gliomas and meningiomas. *Acta Neuropathol (Berl)* 66:245–252
192. Benda P, Sameda K, Messer J, Sweet WH (1971) Morphological and immunochemical studies of the rat glial tumours and clonal strains propagated in cultures. *J Neurosurg* 34:310–323
193. Benedek L, Juba A (1941) Über das Mikroglom. *Dtsch Z Nervenheilkd* 152:159–163
194. Benedetti A, Cecotto C (1961) Aspetti clinico-radiologici del neurinoma del nervo facciale a sviluppo intracranico. *Min Neurochir* 5:105–110
195. Benedict WF, Xu H-J, Hu S-X, Takahashi R (1990) Role of the retinoblastoma gene in the initiation and progression of human cancer. *J Clin Invest* 85:988–993
196. Bennett JP, Rubinstein LJ (1984) The biological behavior of primary cerebral neuroblastoma: a reappraisal of the clinical course in a series of 70 cases. *Ann Neurol* 16:21–27
197. Bennett MJ, Timperley WR, Taylor CB, Hill AS (1977) Isoenzymes of hexokinase in the developing, normal and neoplastic human brain. *Eur J Cancer* 14:189–193
198. Berard-Badier M, Payan M, Colomb H (1961) Kyste dermoïde du IV ventricule chez un sujet présentant depuis 20 ans des troubles mentaux. Etude anatomo-pathologique. *Acta Neuropathol (Berl)* 1:159–167
199. Berg NO, Lindgren M (1958) Time-dose relationship and morphology of delayed radiation lesions of the brain in rabbits. *Acta Radiol Suppl* 167:1–118
200. Berger MS, Wilson CB (1985) Epidermoid cysts of the posterior fossa. *J Neurosurg* 62:214–219
201. Berger MS, Edwards MSB, Wara WM, Levin VA, Wilson CB (1983) Primary cerebral neuroblastoma: long-term follow-up review and therapeutic guidelines. *J Neurosurg* 59:418–442
202. Berger S, Deliganis AV, Dobbins J, Keles GE (1994) The effect of extent of resection on recurrence in patients with low grade cerebral hemisphere gliomas. *Cancer* 6:1784–1791
203. Bergstrand H (1932) Über das sogenannte Astrocytom des Kleinhirns. *Virchows Arch A* 287:538–552
204. Bergstrand H (1933) Über das Gliom in den Grosshirnhemisphären. *Virchows Arch A* 287:797–822
205. Bergstrand H (1937) Weiteres über sogenannte Kleinhirnaströzytome. *Virchows Arch A* 299:725–739
206. Bergstrand H, Olivecrona H, Tönnis W (1936) Gefässemissbildungen und Gefässgeschwülste des Gehirns. Thieme, Leipzig
207. Berkheiser SW (1956) Oligodendrogliomas in the young age group. *J Neurosurg* 13:170–175
208. Bernabò-Brea G (1957) La carcinosi leptomeningea (Meningite carcinomatosa). *Sist Nerv* 1:20–32

209. Bernardis A, Haase VH, Murthy AE, Menon A, Hannigan GE, Gusella JF (1992) Complete human NF1 cDNA sequence: two alternatively spliced mRNAs and absence of expression in a neuroblastoma line. *DNA and Cell Biology* 11:727-734
210. Bernardis A, Snijders AJ, Hannigan GE, Murthy AE, Gusella JF (1993) Mouse neurofibromatosis type 1 cDNA sequence reveals high degree of conservation of both coding and non-coding mRNA segments. *Hum Mol Gene* 2:645-650
211. Bernell W, Kepes J, Scitz E (1972) The late malignant recurrence of a childhood cerebellar astrocytoma. Reported two cases. *J Neurosurg* 37:470-474
212. Bernstein M, Gutin PH (1981) Interstitial radiation of brain tumors: A review. *Neurosurgery* 9:741-750
213. Bernstein M, Perrin R, Platss M, Simpson W (1984) Reduction-induced cerebellar chondrosarcoma. Case report. *J Neurosurg* 61:174-177
214. Bernstein M, Laperriere N, Leung P, McKenzie S (1990) Interstitial brachytherapy for malignant brain tumors: preliminary results. *Neurosurgery* 26:371-380
215. Bernstein M, Cabantog A, Laperriere N, Leung P, Thomason C (1995) Brachytherapy for recurrent single brain metastasis. *Canad J Neurol Sci* 22:13-16
216. Berry AD, Reintjes SL, Kepes JJ (1988) Intracranial malignant fibrous histiocytoma with abscess-like tumor necrosis. *J Neurosurg* 69:780-784
217. Berry MP, Simpson WJ (1981) Radiation therapy in the management of primary malignant lymphoma of the brain. *Int J Radiat Oncol Biol Phys* 7:55-59
218. Berry MP, Jenkin DT, Keen CW, Nair BD, Simpson WJ (1981) Radiation treatment for medulloblastoma. A 21-year review. *J Neurosurg* 55:43-51
219. Berry RG, Schlezinger NS (1959) Rathke's cleft cysts. *Arch Neurol* 1:48-58
220. Bertolotto A, Giordana MT, Magrassi ML, Mauro A, Schiffer D (1982) Glycosaminoglycans in human cerebral tumors. Part I. Biochemical findings. *Acta Neuropathol (Berl)* 58:115-119
221. Bertolotto A, Magrassi ML, Orsi L, Sitia C, Schiffer D (1986) Glycosaminoglycan changes in human gliomas. A biochemical study. *J Neurooncol* 4:43-48
222. Bertrand F, Altschul R (1927) Le métabolisme cérébral du calcium. Etude histologique. *Rev Neurol* 2:241-261
223. Bertrand I, Mannen H (1960) Etudes des réactions vasculaires dans les astrocytomes. *Rev Neurol* 102:3-19
224. Best PV (1963) Metastatic carcinoma in a meningioma. Report of a case. *J Neurosurg* 20:892-894
225. Best PV (1974) Posterior fossa medulloepithelioma. *J Neurol Sci* 22:511-518
226. Best PV (1974) A medulloblastoma-like tumor with melanin formation. *J Pathol* 110:109-123
227. Bestle J (1968) Extragonadal endodermal sinus tumors originating in the region of the pineal gland. *Acta Pathol Microbiol Scand* 74:214-222
228. Betz AL, Firth JA, Goldstein GW (1980) Polarity of the blood-brain barrier: distribution of enzymes between the luminal and antiluminal membranes of brain capillary endothelial cells. *Brain Res* 192:17-28
229. Bidder A (1882) Osteom der corpus striatum bei hemiplegia infantilis. *Virchows Arch A* 88:91-98
230. Bieber CB, Reitz BA, Jamieson SW, Oyer PE, Stinson EB (1980) Malignant lymphoma in cyclosporin A treated allograft recipients. *Lancet* 2:43-45
231. Biegel JA, Rorke LB, Parker RJ, Sutton LN, Shut L, Bonner K, Emanuel BS (1989) Isochromosome 17q in primitive neuroectodermal tumors of the central nervous system. *Genes Chromosomes Cancer* 1:139-147
232. Biegel JA, Rorke LB, Packer RJ, Emanuel BS (1990) Monosomy 22 in rhabdoid or atypical tumors of the brain. *J Neurosurg* 73:710-714
233. Biegel JA, Burk CD, Barr FC, Emanuel BS (1992) Evidence for a 17p tumor related loci distinct from p53 in pediatric primitive neuroectodermal tumors. *Cancer Res* 52:3391-3395
234. Bielschowsky MV (1914) Über Tuberosäre Sklerose und ihre Beziehungen zur Recklinghausen Krankheit. *Z Gesamte Neurol Psychiatry* 26:133-155
235. Biernat W, Aguzzi A, Sure U, Grant JW, Kleihues P, Hegl M (1995) Identical mutations of the p53 tumor suppressor gene in the gliomatous and the sarcomatous components of gliosarcomas suggest a common origin from glial cells. *J Neuropathol Exp Neur* 54:651-656

236. Bignami A, Asher R (1992) Some observations on the localization of hyaluronic acid in adult, newborn and embryonal rat brain. *Int J Dev Neurosci* 10:45–57
237. Bignami A, Dahl D (1974) Astrocyte specific protein and radial glia cerebral cortex of newborn rat. *Nature* 252:55–56
238. Bignami A, Dahl D (1974) Astrocyte-specific protein and neuroglia differentiation. An immunofluorescence study with antibodies to the glial fibrillary acidic protein. *J Comp Neurol* 153:27–38
239. Bignami A, Dahl D (1986) Brain-specific hyaluronate-binding protein. A product of white matter astrocytes? *J Neurocytol* 15:671–679
240. Bignami A, De Matteis A (1956) La malattia di Lhermitte e Duclos del cervelletto (ganglioneuroma displastico). *Riv Anat Pat Oncol* 11:523–538
241. Bignami A, Raju T, Dahl D (1982) Localization of vimentin the nonspecific intermediate filament protein in embryonal glia and in early differentiating neurons. *Dev Biol* 91:286–295
242. Bigner DD (1982) The biology of gliomas: potential clinical implications of glioma cellular heterogeneity. *Neurosurgery* 9:320–326
243. Bigner DD, Pegram CN (1976) A review of virus-induced experimental brain tumors and of the putative associations of viruses with human brain tumors. *Adv Neurol* 15:57–83
244. Bigner DD, Bigner SH, Pontèn J, Westermarck B, Mahaley MS, Ruoslahti E, Herschman H, Eng LF, Wikstrand CJ (1981) Heterogeneity of genotypic and phenotypic characteristics of fifteen permanent cell lines derived from human gliomas. *J Neuropathol Exp Neurol* 40:201–229
245. Bigner SH, Vogelstein B (1990) Cytogenesis and molecular genetics of malignant gliomas and medulloblastoma. *Brain Pathol* 1:12–18
246. Bigner SH, Mark J, Mahaley MS, Bigner DD (1984) Pattern of the early, gross chromosomal changes in malignant human gliomas. *Hereditas* 101:103–113
247. Bigner SH, Wong AJ, Mark J, Muhlabier LH, Kinzler KW, Vogelstein B, Bigner DD (1987) Relationship between gene amplification and chromosomal deviations in malignant human gliomas. *Cancer Genet Cytogenet* 29:165–170
248. Bigner SH, Burger PC, Wong AJ, Werner MH, Hamilton SR, Muhlabier LH, Vogelstein B, Bigner BB (1988) Gene amplification in malignant human gliomas: clinical and histopathologic aspects. *J Neuropathol Exp Neurol* 47:191–205
249. Bigner SH, Mark J, Burger PC, Mahaley MS, Bullard DE, Muhlabier LH, Bigner DD (1988) Specific chromosomal abnormalities in malignant human gliomas. *Cancer Res* 48:405–411
250. Bigner SH, Mark J, Friedman HS, Biegel JA, Bigner DD (1988) Structural chromosomal abnormalities in human medulloblastoma. *Cancer Genet Cytogenet* 30:91–101
251. Bigner SH, Friedman HS, Oakes WJ, Vogelstein B, Bigner DD (1990) Amplification of the C-MYC gene in medulloblastoma cell lines and xenografts. *Cancer Res* 50:2347–2350
252. Bigner SH, Mark J, Bigner DD (1990) Cytogenetics of human brain tumors. *Cancer Genet Cytogenet* 47:141–154
253. Bigner DD, Brown M, Coleman RE, Friedman AH, Friedman HS, McLendon RE, Bigner SH, Zhao X-G, Wikstrand CJ, Pegram CN, Kerby T, Zalutsky MR (1995) Phase I studies of treatment of malignant gliomas and neoplastic meningitis with <sup>131</sup>I-radiolabeled monoclonal antibodies anti-tenascin 81C6 and anti-chondroitin proteoglycan sulfate Mel-14F (ab')<sub>2</sub> - a preliminary report. *J Neurooncol* 24:109–122
254. Bijlsma EK, Merel P, Bosh DA, Westerveld A, Dalattre O, Thomas G, Huselbos TJM (1994) Analysis of mutations of the SCH gene in schwannomas. *Genes Chrom Cancer* 11:7–14
255. Bindal RK, Sawaya R, Leavens ME, Hess KR, Taylor SH (1995) Reoperation for recurrent metastatic brain tumors. *J Neurosurg* 83:600–604
256. Bingas B (1964) Das monstrocelluläre Sarkom des Gehirns *Arch Psych Nervenkr* 205:223–236
257. Bishop JM (1983) Cellular oncogenes and retroviruses. *Am Rev Biochem* 52:301–354
258. Bishop JM (1991) Molecular themes in oncogenesis. *Cell* 64:235–248
259. Bishop MB, de la Monte SM (1989) Dual lineage of astrocytomas. *Am J Pathol* 135:517–527
260. Bitoh S, Obashi J, Kobayashi Y (1986) Primary ectopic extracalvarial meningioma. *Surg Neurol* 25:591–594
261. Bjerkvig R, Laerum OD, Mella O (1986) Glioma cell interactions with fetal rat brain aggregates in vitro and with brain tissue in vivo. *Cancer Res* 46:4071–4079

262. Bjornsson J, Scheithauer BW, Okazaki H, Lecch RW (1985) Intracranial germ cell tumors: pathobiologic and immunohistochemical aspects of 70 cases. *J Neuropathol Exp Neurol* 44:32–46
263. Bjornsson J, Scheithauer BW, Leech RW (1986) Primary intracranial choriocarcinoma: a case report. *Clin Neuropathol* 5:242–245
264. Black BK, Smith DE (1950) Nasal glioma. Two cases with recurrence. *Arch Neur Psych* 64:614–630
265. Black PML, Carroll R, Glowcka D, Riley K, Dashner K (1994) Platelet-derived growth factor expression and stimulation in human meningiomas. *J Neurosurg* 81:388–393
266. Bland JOW, Russell DS (1938) Histological types of meningioma. *J Pathol* 47:291–309
267. Blarucha NE, Raven RH, Schoenberg BS (1985) Primary malignant nervous system neoplasms: birth cohort effect in the elderly. *Arch Neurol* 42:1061–1062
268. Blasberg R, Groothuis D (1986) Chemotherapy of brain tumors: physiological and pharmacokinetic considerations. *Semin Oncol* 13:70–82
269. Blasberg RG, Groothuis DR, Molnar P (1981) The application of quantitative autoradiographic measurements in experimental brain tumours. *Semin Neurol* 1:203–223
270. Blatt J, Jaffe R, Deutsch M, Adkins JC (1986) Neurofibromatosis and childhood tumours. *Cancer* 57:1125–1129
271. Bleehen NM, Ford JM (1993) Radiotherapy, hyperthermy, and photodynamic therapy for central nervous system tumors. *Curr Opin Oncol* 5(3):458–463
272. Bleyer WA, Griffin TW (1980) White matter necrosis, mineralizing microangiopathy and intellectual abilities in survivors of childhood leukemia: associations with central nervous system irradiation and methotrexate therapy. In: Gilbert HA, Kagan AR (eds) *Radiation damage to the nervous system*. Raven, New York, pp 155–174
273. Blinkey W, Vakili ST, Worth R (1982) Paraganglioma of the cauda equina. *J Neurosurg* 56:275–279
274. Bloom HJG (1979) Intracranial secondary carcinomas and disseminating glioma: treatment and prognosis. In: Whithouse JMA, Kay HEM (eds) *CNS complications of malignant disease*. University Park, Baltimore, pp 329–359
275. Bloom HJG, Bessell EM (1990) Medulloblastoma in adults: a review of 47 patients treated between 1952 and 1981. *Int J Radiat Oncol Biol Phys* 18:760–772
276. Bloom W, Fawcett DW (1975) *A textbook of histology*, 10th edn., Saunders, Philadelphia, p 172
277. Bobola MS, Blank A, Berger MS, Silber JR (1995) Contribution of O-6-methylguanine-DNA methyltransferase to monofunctional alkylating-agent resistance in human brain tumor-derived cell lines. *Mol Carcinog* 13:70–80
278. Bobola MS, Berger MS, Silber JR (1995) Contribution of O-6-methylguanine-DNA methyltransferase to resistance to 1,3-(2-chloroethyl)-1-nitrosourea in human brain tumor-derived cell lines. *Mol Carcinog* 13:81–88
279. Bochnik HJ (1953) Nekrosekalk und kalzifizierende Organisation im Gehirn. *Dtsch Z Nervenheilkd* 169:358–382
280. Böck P, Jellinger K (1981) Detection of glycosaminoglycans in human gliomas by histochemical methods. *Acta Neuropathol (Berl) Suppl* 7:81–84
281. Boden JB (1950) Radiation myelitis of the brain stem. *J Fac Radiol* 2:79–94
282. Bodmer S, Siepl C, Fontana A (1989) Immunological aspects of gliomas. In: Broggi G, Gerosa MA (eds) *Cerebral gliomas*. Elsevier, Amsterdam, pp 69–75
283. Boesel CP, Suhan JP (1979) A pigmented choroid plexus carcinoma: histochemical and ultrastructural findings. *J Neuropathol Exp Neurol* 38:177–186
284. Boesel CP, Suhan JP, Bradel EJ (1978) Ultrastructure of primitive neuroectodermal neoplasms of the central nervous system. *Cancer* 42:194–201
285. Boesel CP, Suhan JP, Sayers MP (1978) Melanotic medulloblastoma. Report of a case with ultrastructural findings. *J Neuropathol Exp Neurol* 37:531–543
286. Bofin PJ, Ebels E (1963) A case of medulloblastoma. *Acta Neuropathol (Berl)* 2:309–311
287. Bogdahn U (1983) Chemosensitivity of malignant human brain tumors. Preliminary results. *J Neurooncol* 1:149–166
288. Bogdahn U, Bogdahn S, Mertens HG, Dommasch D, Wodarz R, Wünsch PH, Kühl P, Richter E (1986) Primary non-Hodgkin's lymphomas of the CNS. *Acta Neurol Scand* 73:602–614

289. Boggan JE, Rosenblum ML, Wilson CB (1979) Neurilemmoma of the fourth cranial nerve: case report. *J Neurosurg* 50:519–521
290. Boggan JE, Bolger C, Edwards MSB (1985) Effect of hematoporphyrin derivative photoradiation therapy on survival in the rat 9L gliosarcoma brain-tumor model. *J Neurosurg* 63:917–921
291. Böhling T, Haltia M, Rosenlöf K, Fyhrquist F (1987) Erythropoietin in capillary hemangioblastoma. An immunohistochemical study. *Acta Neuropathol (Berl)* 74:324–328
292. Böker DK, Wassman H, Solymosy L (1983) Paragangliomas of the spinal canal. *Surg Neurol* 19:461–468
293. Böker DK, Kalff R, Gullotta F, Weekes-Seifert S, Möhrer U (1984) Mononuclear infiltrates in human intracranial tumors as a prognostic factor. Influence of preoperative steroid treatment. I. Glioblastoma. *Clin Neuropathol* 3:143–147
294. Bolliger A (1963) Multiple glioma. *Confinia Neurol* 23:406–430
295. Bonebrake RA, Siqueira EB (1964) The familial occurrence of solitary hemangioblastoma of the cerebellum. *Neurology* 14:733–743
296. Bonnal J, Born JD, Tremoulet M (1979) Meningiomes multiples intracraniens. *Neurochirurgie* 25:78–83
297. Bonnin JM, Garcia JM (1987) Primary malignant non-Hodgkin's lymphoma in central nervous system. *Pathol Ann* 22:353–375
298. Bonnin JM, Rubinstein LJ (1984) Immunohistochemistry of the central nervous system tumors. Its contributions to neurosurgical diagnosis. *J Neurosurg* 60:121–133
299. Bonnin JM, Rubinstein LJ (1989) Astroblastomas: a pathological study of 23 tumors, with a postoperative follow-up in 13 patients. *Neurosurgery* 25:6–13
300. Bonnin JM, Peña CE, Rubinstein LJ (1983) Mixed capillary hemangioblastoma and glioma. A redefinition of the "angioglioma". *J Neuropathol Exp Neurol* 42:504–516
301. Bonnin JM, Rubinstein LJ, Palmer NF, Beckwith JB (1984) The association of embryonal tumors originating in the kidney and in the brain. A report of seven cases. *Cancer* 54:2137–2146
302. Bonnin JM, Rubinstein LJ, Papasozomenos S, Marangos PJ (1984) Subependymal giant cell astrocytoma. Significance and possible cytogenetic implications of an immunohistochemical study. *Acta Neuropathol (Berl)* 62:185–193
303. Bonnin JM, Wilson ER, Garcia JH (1989) Medulloblastoma with neuronal, glial, striated muscle and pigment epithelium differentiation. *Canad J Neurol Sci* 16:227–235
304. Boogerd W, Hart AAM, van der Sande JJ, Engelsman E (1991) Meningeal carcinomatosis in breast cancer. Prognostic factors and influence of treatment. *Cancer* 67:1685–1695
305. Bookwalter W, Selker RG, Schiffer L, Randall M, Iannuzzi D, Kristofik M (1986) Brain-tumor cell kinetics correlated with survival. *J Neurosurg* 65:795–798
306. Bordi L, Compton J, Symon I (1989) Trigeminal neuroma: a report of eleven cases. *Surg Neurol* 31:272–276
307. Borit A (1969) Embryonal carcinoma of the pineal region. *J Pathol* 97:165–168
308. Borit A, Blackwood W (1979) Pineocytoma with astrocytomatous differentiation. *J Neuropathol Exp Neurol* 38:253–258
309. Borit A, McIntosh GC (1981) Myelin basic protein and glial fibrillary acid protein in human fetal brain. *Neuropathol Appl Neurobiol* 7:279–287
310. Borit A, Richardson EP Jr (1982) The biological and clinical behaviour of pilocytic astrocytomas of the optic pathways. *Brain* 105:161–187
311. Borit A, Blackwood W, Mair WGP (1980) The separation of pineocytoma from pineoblastoma. *Cancer* 1408–1418
312. Borovich B, Doron Y (1986) Recurrence of intracranial meningiomas: the role played by regional multicentricity. *J Neurosurg* 64:58–63
313. Bosch DA (1977) Short and long term effects of methyl- and ethylnitrosourea (MNU & ENU) on the developing nervous system of the rat. II Short term: concluding remarks on chemical neuro-oncogenesis. *Acta Neurol Scand* 55:106–122
314. Bostroem E (1897) Über die pialen Epidermoide, Dermoide und Lipome und duralen Dermoides. *Zbl Allg Pathol* 8:1–98
315. Bouchard J (1966) Radiation therapy of tumours and diseases of the nervous system. Lea and Febiger, Philadelphia, pp 97–98
316. Bouillot P, Pellissier JF, Devictor B, Graziani N, Bianco N, Grisoli F, Figarella-Branger D (1994) Quantitative imaging of estrogen and progesterone receptors, estrogen-regulated pro-

- tein, and growth fraction: immunocytochemical assays in 52 meningiomas. *J Neurosurg* 81:765–773
317. Bourdon MA, Coleman RE, Bigner DD (1984) The potential of monoclonal antibodies as carriers of radiation and drugs for immunodetection and therapy of brain tumors. *Prog Exp Tumor Res* 28:79–100
  318. Boyazis RM, Martin L, Bouteille M, Guazzi GC, Manacorda A (1967) Images histochimiques et ultrastructurales dans un cas de sclérose en plaque associée à un spongioblastome. *Riv Patol Nerv Ment* 88:1–20
  319. Boyd HR (1966) Iatrogenic intraspinal epidermoid. Report of a case. *J Neurosurg* 24:105–107
  320. Boykin FC, Cowen D, Iannucci ChAJ, Wolf A (1954) Subependymal glomerate astrocytomas. *J Neuropathol Exp Neurol* 13:30–49
  321. Brada M (1989) Back to the future – radiotherapy in high grade gliomas. *Br J Cancer* 60:1–4
  322. Bradac GB, Ferszt R, Bender A, Schörner W (1986) Peritumoral edema in meningiomas. A radiological and histological study. *Neuroradiology* 28:304–312
  323. Bradac GB, Ferszt R, Kendall BE (1990) Cranial meningiomas. Diagnosis, biology, therapy. Springer, Berlin Heidelberg New York
  324. Bradac GB, Soffietti R, Riva A, Stura G, Sales S, Schiffer D (1992) Selective intra-arterial chemotherapy with BCNU in recurrent malignant gliomas. *Neuroradiology* 34:73–76
  325. Brander WL, Turner DR (1975) Extracranial metastasis from a glioma in the absence of surgical intervention. *J Neurol Neurosurg Psychiatry* 38:1133–1135
  326. Brant-Zawadzki M, Badami JP, Mills CM, Norman D, Newton TH (1984) Primary intracranial tumor imaging: a comparison of magnetic resonance and CT. *Radiology* 150:435–440
  327. Brem S, Tsanacis AM, Zagzap D (1990) Anticopper treatment inhibits pseudopodial profusion and the invasive spread of 9L gliosarcoma cells in the rat brain. *Neurosurgery* 26:391–396
  328. Brem H, Piantadosi S, Berger PC, Welker M, Selker R, Vick NA, Black K, Sisti M, Brem S, Motz G, Muller P, Morawetz R, Schold SC (1995). Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. *Lancet* 345:1008–1012
  329. Brenner ED (1989) Liposomal encapsulation: making old and new drugs do new tricks. *J Natl Cancer Inst* 1436–1438
  330. Bressler JP, Cole R, De Vellis J (1983) Neoplastic transformation of newborn rat oligodendrocytes in culture. *Cancer Res* 43:709–715
  331. Breuer AC, Blank NK, Schoene WC (1978) Multifocal pontine lesions in cancer patients treated with chemotherapy and CNS radiotherapy. *Cancer* 41:2112–2120
  332. Brightman MW, Paley SL (1963) The fine structure of the ependyma in the brain of the rat. *J Cell Biol* 19:415–439
  333. Brignolio F, Favero M (1984) Considerations on the malignancy of papillary meningioma. Clinico-pathological study of eight cases. *Zbl Neurochir* 45:79–84
  334. Brihaye J, Martin P (1961) Analyse de 172 tumeurs métastatiques du système nerveux. *Neurochirurgie* 7:147–151
  335. Brihaye J, Mage J, Marin P (1958) Kystes épidermiques crâniens. *Acta Neurol Psychiatr Belg* 58:557–596
  336. Brihaye J, Perier O, Sténuit J (1963) Multiple sclerosis associated with a cerebral glioma. *J Neuropathol Exp Neurol* 22:128–137
  337. Britt RH, Pounds DW, Lyons BE (1984) Feasibility of treating malignant brain tumors with focused ultrasound. *Prog Exp Tumor Res* 28:232–245
  338. Broadwell RD (1989) Transcytosis of macromolecules through the blood–brain barrier. A critical appraisal and cell biological perspective. *Acta Neuropathol (Berl)* 79:117–128
  339. Broadwell RD, Balin BJ, Salzman M (1988) Transcytosis of blood-borne protein through the blood–brain barrier. *Proc Natl Acad Sci USA* 85:632–636
  340. Broders AC (1920) Squamous cell epithelioma of the lip: a study of five hundred and thirty-seven cases. *JAMA* 74:656–664
  341. Broders AC (1926) Carcinoma: grading and practical application. *Arch Pathol* 2:376–381
  342. Brodeur GM (1990) Neuroblastoma – clinical applications of molecular parameters. *Brain Pathol* 1:47–54

343. Brodeur GM, Seeger RC, Schwab M, Varmus HE, Bishop JM (1984) Amplification of N-myc in untreated human neuroblastomas correlates with advanced disease stage. *Science* 224:1121–1124
344. Broker W, Dralle H, Husselmann H, Bay V, Brassow M. (1980) Immunohistochemical analysis of thyroglobulin synthesis in thyroid carcinoma. *Virchows Arch (A)* 385:187–200
345. Brooks D, Beaney R, Thomas D (1986) The role of positron emission tomography in the study of cerebral tumors. *Semin Oncol* 13:83–93
346. Brooks JJ (1982) Immunohistochemistry of soft tissue tumors: myoglobin as a tumor marker for rhabdomyosarcoma. *Cancer* 50:1757–1763
347. Brooks JJ, Livolsi A, Trojanowski JQ (1987) Does chondroid chordoma exist? *Acta Neuropathol (Berl)* 72:229–235
348. Brooks WH (1972) Geographic clustering of brain tumors in Kentucky. *Cancer* 30:923–926
349. Brooks WH, Netsky MG, Normansell DE, Horwitz DA (1972) Depressed cell-mediated immunity in patients with primary intracranial tumors. *J Exp Med* 136:1631–1647
350. Brooks WH, Roszman TL, Mahaley MS, Woosley RE (1977) Immunobiology of primary intracranial tumors. II. Analysis of lymphocyte subpopulations in patients with primary brain tumors. *Clin Exp Immunol* 29:61–66
351. Brooks WH, Markesbery WR, Gupta GD, Roszman TC (1978) Relationship of lymphocyte invasion and survival of brain tumor patients. *Ann Neurol* 4:219–224
352. Brooks WH, Latta RB, Mahaley MS, Roszman TL, Dudka L, Skagg C (1981) Immunobiology of primary intracranial tumors. Part 5: Correlation of lymphocyte index and clinical status. *J Neurosurg* 54:331–337
353. Broth J, Scuvee-Moreau J, Dresse A (1978) Correlation entre le caractère epileptogène d'un foyer lésionnel et la présence dans celui-ci d'"astrocytes actifs" (présentant une activité très intense des deshydrogenases et de l'alpha-glucon-phosphorylase). Etude chez l'homme et l'animal. *Acta Neurol Belg* 78:267–278
354. Brown JS (1985) Glomus jugulare tumors revisited: a ten-year statistical follow-up of 231 cases. *Laryngoscope* 95:284–288
355. Brown MT, Mc Clendon RE, Gockerman JP (1995) Primary central nervous system lymphoma with systemic metastasis: case report and review. *J Neurooncol* 23:207–221
356. Browne TR, Adams RD, Robertson GH (1976) Hemangioblastoma of the spinal cord. Review and report of five cases. *Arch Neurol* 33:435–441
357. Brozman M (1978) Immunohistochemical analysis of formaldehyde and trypsin-treated material. *Acta Histochem* 63:251–260
358. Bruce JW, Criscuolo GR, Merrill MJ, Moquin RR, Blocklock JB, Oldfield EM (1987) Vascular permeability induced by a protein of malignant brain tumors: inhibition by dexamethasone. *J Neurosurg* 67:880–884
359. Brucher JM (1964) The classification and diagnosis of intracranial sarcomas. *Acta Neurochir (Wien)* 10:190–200
360. Brucher JM, Cervós-Navarro J (1960) La carcinomatose méningée. Etude anatomo-clinique de 11 cas. *Acta Neurol Psychiatr Belg* 60:368–398
361. Bruni JE, Del Bigio MR, Clattenburg RE (1985) Ependyma: normal and pathological. A review of the literature. *Brain Res Rev* 9:1–19
362. Bruni P, Esposito S, Greco R, Oddi G (1984) Solitary intracerebral schwannoma in von Recklinghausen's disease. *Surg Neurol* 22:300–304
363. Bruton CJ (1988) The neuropathology of temporal lobe epilepsy. Oxford University Press, Oxford (Mandsley Monographs 31)
364. Bryans WA (1959) Mitotic activity in the brain of the adult rat. *Anat Res* 133:65–71
365. Buchberg AM, Cleveland LS, Jenkins NA, Copeland NG (1990) Sequence nomology shared by neurofibromatosis type-1 gene and IRA-1 and IRA-2 negative regulators of the RAS cyclic AMP pathway. *Nature* 347:291–294
366. Buchpiguel CA, Alavi JB, Alavi A, Kenyon LC (1995) PET versus SPECT in distinguishing radiation necrosis from tumor recurrence in the brain. *J Nucl Med* 36:159–164
367. Buckner JC (1991) The role of chemotherapy in the treatment of patients with brain metastases from solid tumors. *Cancer Metastasis Rev* 10:335–341
368. Buckwalter JA, Turner JH, Gamber HH, Raterman K, Soper RT, Knowler LA (1959) Psychoses, intracranial neoplasms, and genetics. *Arch Neurol Psychiatry* 81:480–485



369. Bucy PC, Gustafson WA (1939) Structure, nature and classification of cerebellar astrocytomas. *Am J Cancer* 35:327–353
370. Bucy PC, Gustafson WA (1939) Intradural lipoma of the spinal cord. *Zbl Neurochir* 3:341–349
371. Bucy PC, Jerva MJ (1962) Primary epidural spinal lymphosarcoma. *J Neurosurg* 19:142–152
372. Budka H (1974) Intracranial lipomatous hamartomas (intracranial “lipomas”). A study of 13 cases including combinations with medulloblastoma, colloid and epidermoid cysts, angiomas and other malformations. *Acta Neuropathol (Berl)* 28:205–222
373. Budka H (1975) Partially resected and irradiated cerebellar astrocytoma of childhood: malignant evolution after 28 years. *Acta Neurochir (Wien)* 32:139–146
374. Budka H (1982) Hyaline inclusions (pseudopsammoma bodies) in meningiomas: immunocytochemical demonstration of epithelial-like secretion of secretory component and immunoglobulins A and M. *Acta Neuropathol (Berl)* 56:294–298
375. Budka H (1982) Pathology of encephalopathies induced by treatment or prophylaxis of neoplastic lesions of the nervous system. In: Hildebrand J, Gangji D (eds) *Treatment of neoplastic lesions of the nervous system*. Pergamon, Oxford, pp 45–56
376. Budka H (1986) Non glial specificities of immunocytochemistry for the glial fibrillary acidic protein (GFAP). Triple expression of GFAP, vimentin and cytokeratins in papillary meningioma and metastasizing renal carcinoma. *Acta Neuropathol (Berl)* 72:43–54
377. Budka H, Pantucek F (1973) Primäre diffuse Melanoblastosen der Meningen und neurokutane Melanosen. *Neurochirurgia (Wien)* 16:90–98
378. Budka H, Podreka I, Reisser T, Zeiler K (1980) Diagnostic and pathomorphological aspects of glioma multiplicity. *Neurosurg Rev* 3:233–241
379. Bueno JG, Esteban HN, Lopez CB, Puentes MLF (1977) Congenital meningioma. *Childs Brain* 3:304–308
380. Bulfone A, Puelles L, Porteus MH, Frohman MA, Martin GR, Rubenstein JLR (1993) Spatially restricted expression of *Dlx-1*, *Dlx-2* (*Tes-1*), *Gbx-2*, and *Wnt-3* in the embryonic day 12.5 mouse forebrain defines potential transverse and longitudinal segmental boundaries. *J Neurosci* 13:3155–3172
381. Bullard DE, Bigner DD (1980) Animal Models and Virus Induction of Tumours. In: Thomas DGT, Graham DI (eds) *Brain tumours*. Butterworths, London, pp 51–84
382. Bullard DE, Bigner DD (1985) Applications of monoclonal antibodies in the diagnosis and treatment of primary brain tumors. *J Neurosurg* 63:2–16
383. Bullard DE, Rawlings CE, Phillips B et al (1987) Oligodendroglioma. An analysis of the value of radiation therapy. *Cancer* 60:2179–2188
384. Bunin G (1987) Racial patterns of childhood brain cancer by histologic type. *J Natl Cancer Inst* 78:875–880
385. Bunin GR, Kuijten RR, Buckley JD, Rorke LB, Meadows A (1993) Relation between maternal diet and subsequent primitive neuroectodermal brain tumors in young children. *N Engl J Med* 329:536–541
386. Burch JD, Craib KJP, Choi BCK, Miller AB, Risch HA, Howe GR (1987) An exploratory case-control study of brain tumors in adults. *J Natl Cancer Inst* 78:601–609
387. Burger PC (1989) The grading of astrocytomas and oligodendrogliomas. In: Fields WS (ed) *Primary brain tumors. A review of histologic classification*. Springer, Berlin Heidelberg New York, pp 171–180
388. Burger PC, Green SB (1987) Patient age, histologic features, and length of survival in patients with glioblastoma multiforme. *Cancer* 59:1617–1625
389. Burger PC, Kleihues P (1989) Cytologic composition of the untreated glioblastoma multiforme: a post mortem study of eighteen cases. *Cancer* 63: 2014–2023
390. Burger PC, Vollmer RT (1980) Histologic factors of prognostic significance in the glioblastoma multiforme. *Cancer* 46:1179–1186
391. Burger PC, Mahaley MS Jr, Dudka L, Vogel FS (1979) The morphologic effects of radiation administered therapeutically for intracranial gliomas. A postmortem study of 25 cases. *Cancer* 44:1256–1272
392. Burger PC, Kamenar E, Schold SC, Fay JW, Phillips GL, Herzig GP (1981) Encephalomyelopathy following high-dose BCNU therapy. *Cancer* 48:1318–1327

393. Burger PC, Dubois PJ, Schold SC, Smith KR, Odom GL, Crafts DC, Giangaspero F (1983) Computerized tomographic and pathologic studies of the untreated, quiescent and recurrent glioblastoma. *J Neurosurg* 58:159–169
394. Burger PC, Vogel FS, Green SB, Strike TA (1985) Glioblastoma multiforme and anaplastic astrocytoma: Pathologic criteria and prognostic implications. *Cancer* 56:1106–1111
395. Burger PC, Shibata C, Kleihues P (1986) The use of the monoclonal antibody Ki-67 in the identification of proliferating cells: application to surgical neuropathology. *Am J Surg Pathol* 10:611–617
396. Burger PC, Makek M, Kleihues P (1986) Tissue polypeptide antigen staining of the cordoma and notochordal remnants. *Acta Neuropathol (Berl)* 70:269–272
397. Burger PC, Rawlings CE, Cox EB (1987) Clinicopathologic correlations in the oligodendroglioma. *Cancer* 59:1345–1352
398. Burger PC, Grahmann PC, Bliestle A, Kleihues P (1987) Differentiation in the medulloblastoma: a histological and immunohistochemical study. *Acta Neuropathol (Berl)* 73:115–123
399. Burger PC, Shibata T, Aguzzi A, Kleihues P (1988) Selective induction by Nitrosoethylurea of oligodendrogliomas in fetal forebrain transplants. *Cancer Res* 48:2871–2875
400. Burger PC, Scheithauer BW, Vogel FS (1991) Surgical pathology of the nervous system and its coverings, 3rd edn. Churchill Livingstone, New York
401. Burns RJ, Jones AN, Robertson JS (1972) Pathology of radiation myelopathy. *J Neurol Neurosurg Psych* 35:888–898
402. Burstein SD, Kernohan JW, Ullhein A (1963) Neoplasms of the reticuloendothelial system of the brain. *Cancer* 16:289–305
403. Burston J, John R, Spencer H (1962) Myoblastoma of the neurohypophysis. *J Pathol Bacteriol* 83:455–461
404. Busch E, Christensen E (1947) The three types of glioblastoma. *J Neurosurg* 4:200–220
405. Butti G, Giordana MT, Paoletti P, Schiffer D (1982) Multiple primary intracranial tumors of different cell types: association of anaplastic astrocytoma and acoustic neurinoma with review of the literature. *Surg Neurol* 18:336–342
406. Butti G, Gaetani MP, Giordana MT, Paoletti PL (1983) Meningiomas of Meckel's cave. *Surg Neurol* 20:305–309
407. Butti G, Assietti R, Casalone R, Paoletti P (1989) Multiple meningiomas: a clinical, surgical and cytogenetic analysis. *Surg Neurol* 31:255–260
408. Byar DP, Green SB, Strike TA (1983) Prognostic factors for malignant glioma. In: Walker MD (ed) *Oncology of the nervous system*. Nijhoff, Boston, pp 379–396
409. Cabezudo JM, Vaquero J, Areitio E, Martinez R, Garcia de Sola R, Bravo G (1981) Craniopharyngiomas: a critical approach to treatment. *J Neurosurg* 55:371–375
410. Caccamo DV, Herman MM, Rubinstein LJ (1989) An immunohistochemical study of the primitive and maturing elements of human cerebral medulloepitheliomas. *Acta Neuropathol (Berl)* 79:248–254
411. Cairncross JG (1987) The biology of astrocytoma: lessons learned from chronic myelogenous leukemia hypothesis. *J Neurooncol* 5:99–104
412. Cairncross JG, Laperriere NJ (1989) Low-grade glioma. To treat or not to treat? *Arch Neurol* 46:1238–1239
413. Cairncross JG, MacDonald DR (1988) Successful chemotherapy for recurrent malignant oligodendroglioma. *Ann Neurol* 23:360–364
414. Cairncross JG, Mattes MJ, Baresfold HR, Albino AP, Houghton AN, Lloyd KO, Old LJ (1982) Cell surface antigens of human astrocytoma defined by mouse monoclonal antibodies. Identification of astrocyte subset. *Proc Natl Acad Sci USA* 79:5641–5645
415. Cairncross JG, MacDonald DR, Ludwin S, Lee D, Cascino T, Buckner J, Fulton D, Dropcho E, Steward D, Schold C (1994) Chemotherapy for anaplastic oligodendrogliomas. *J Clin Oncol* 12:2013–2021
416. Cajal Ramon y S (1908) Nouvelles observations sur l'évolution des neuroblastes. *Anat Anz* 11:255
417. Cajal Ramon y S (1911) Histologie du système nerveux de l'homme et des Vertébrés. Institut Ramon y Cajal, Madrid, pp. 80–106
418. Cajal Ramon y S (1955) Histologie des système nerveux de l'homme et des vertébrés, vol 2. Maloine, Paris

419. Cajal Ramon y S (1959) Studies on vertebrate neurogenesis. Thomas, Springfield
420. Calabrese P, Parks RE (1980) Chemotherapy of neoplastic disease. In: Gilman AG, Goodman LS, Gilman A (eds) The pharmacological basis of therapeutics. Macmillan, New York, pp 1249–1313
421. Caley DW, Maxwell DS (1970) Development of the blood vessels and extracellular spaces during post-natal maturation of rat cerebral cortex. *J Comp Neurol* 138:31–48
422. Callen DF, Cirocco L, Moore LA (1989) A der(11)t(8,11) in two medulloblastomas. A possible nonrandom cytogenetic abnormality. *Cancer Genet Cytogenet* 38:255–260
423. Calogero JA, Moossy J (1972) Extradural spinal meningiomas. Report of four cases. *J Neurosurg* 37:442–447
424. Calvo W (1954) Tumores encefalomedulares. Estudio morfológico y biológico. *Arch Esp Morfol Suppl* 5:1–173
425. Calvo W (1971) Growth patterns of intracranial neoplasms. In: Minckler J (ed) Pathology of the nervous system, vol 2 McGraw-Hill, New York, pp 1960–1976
426. Camins MB, Cravioto HM, Epstein F, Ransohoff J (1980) Medulloblastoma: an ultrastructural study—evidence for astrocytic and neuronal differentiation. *Neurosurgery* 6:398–411
427. Camp JD (1950) Significance of intracranial calcification in Roentgenologic diagnosis of intracranial neoplasms. *Radiology* 55:659–667
428. Campbell AN, Chan HSL, Becker LE, Daneman A, Park TS, Hoffmann HJ (1984) Extracranial metastases in childhood primary intracranial tumors: A report of 21 cases and review of the literature. *Cancer* 53:974–981
429. Campos MG, Zentner J, Ostertun B, Wolf HK, Schramm J (1993) Anaplastic ganglioglioma: case report and review of the literature. *Neurol Res* 16:317–320
430. Cancilla PA, Zimmermann HM (1965) The fine structure of a cerebellar hemangioblastoma. *J Neuropathol Exp Neurol* 24:621–628
431. Cancilla PA, Morecki R, Hurwitt ES (1964) Fine structure of a recurrent chordoma. *Arch Neurol* 11:289–295
432. Cantley LC, Auger KR, Carpenter C, Duckworth B, Graziani A, Kapeller R, Soltoff S (1991) Oncogenes and signal trasduction. *Cell* 64:281–302
433. Cantor KP, Sontag JM, Heid MF (1986) Patterns of mortality among plumbers and pipefitters. *Am J Ind Med* 10:73–90
434. Capon A, Flament-Durand J, Potvliege R (1966) Deux cas de lipome du corps calleux. *Acta Neurol Psychiatr Belg* 66:9–28
435. Capone PM, Papsidero LD, Croghan GA (1985) Experimental tumoricidal effects of monoclonal antibody against solid breast tumors. *Proc Natl Acad Sci USA* 36:125–132
436. Caputy AJ, McCullough DC, Manz HJ, Patterson K, Hammock MK (1987) A review of the factors influencing the prognosis of medulloblastoma: the importance of cell differentiation. *J Neurosurg* 66:80–87
437. Carbone F, Brihaye J, Drochmans P (1955) Spongioblastome pariéto-occipital et gangliocytome dysplasique du cervelet chez le même malade. *Acta Neurol Psychiatr Belg* 55:568–580
438. Cardauns H (1957) Über ein malignes Plexuspapillom. *Zbl Neurochir* 17:349–353
439. Cardinali DP, Vacas MI, Gejman PV et al (1983) The sympathetic superior cervical ganglia as “little neuroendocrine brains”. *Acta Physiol Lat Am* 33:205–221
440. Carella RJ, Ransohoff J, Newall J (1982) Role of radiation therapy in the management of meningioma. *Neurosurgery* 10:332–339
441. Carmel PW, Antunes JL, Chang CH (1982) Craniopharyngiomas in children. *Neurosurgery* 11:382–389
442. Carrie C, Lasset C, Alapetite C, Haie-Meder C, Hoffstetter S, Demaille MC, Kerr C, Wagner JP, Lagrange JL, Maire JP, Seng SH, Kong Mao YOCT, Muracciole X, Pinto N (1994) Multivariate analysis of prognostic factors in adult patients with medulloblastoma: retrospective study of 156 patients. *Cancer* 74:2352–2360
443. Carson PC, Hellwig CA (1933) Multiple intracranial tumors in children: suprasellar adamantinoma associated with cerebral glioma. *Am J Dis Child* 46:119–131
444. Carter LP, Beggs J, Waggener JD (1972) Ultrastructure of three choroid plexus papillomas. *Cancer* 30:1130–1136
445. Casadei GP, Arrigoni GL, D’Angelo V, Bizzozzero L (1990) Late malignant recurrence of childhood cerebellar astrocytoma. *Clin Neuropathol* 9:295–298

446. Casadei GP, Arrigoni GL, Versari P, Gambacorta M, Giangaspero F (1991) Central neurocytoma. A clinico-pathologic study of five cases. *Tumori* 77:323–327
447. Casalone R, Granata P, Simi P, Tarantino E, Butti G, Buonaguidi R, Faggionato F, Knerich R, Solero L (1987) Recessive cancer genes in meningiomas? An analysis of 31 cases. *Cancer Genet Cytogenet* 27:145–159
448. Cashion EL, Young JM (1971) Intraventricular craniopharyngioma. Report of two cases. *J Neurosurg* 34:84–87
449. Cassirer R, Levy FH (1923) Die Formen der Glioblastose und ihre Stellung zur diffuse Hirnsklerose. *Z Neurol Psychol* 81:290–312
450. Castaigne P, Escourolle R, Poirier J (1966) L'ultrastructure des meningiomes. Etude de 4 cas en microscope electronique. *Rev Neurol* 114:249–261
451. Castellano F, Ruggiero G (1953) Meningiomas of the posterior fossa. *Acta Radiol [Suppl]* 104:146
452. Castelli MG, Butti G, Chiabrando C, Cozzi E, Fanelli R, Gaetani P, Silvani V, Paoletti P (1987) Arachidonic acid metabolic profiles in human meningiomas and gliomas. *J Neurooncol* 5:369–375
453. Catterall MC, Bloom HJG, Ash DV, Walsh L, Richardson A, Uttley D, Gocuing NF, Luvis, P, Chaner B (1980) Fast neutrons compared with megavoltage X-rays in the treatment of patients with supratentorial glioblastoma: a controlled pilot study. *Int J Radiat Oncol Biol Phys* 6:261–266
- 453a. Cattoretti G, Becker MHG, Key G, Dochrow M, Schlüter C, Galle J, Gerdes J (1992) Monoclonal antibodies against recombinant parts of the Ki-67 antigen (MIB-1 and MIB-3) detect proliferating cells in microwave-processed formalin-fixed paraffin sections. *J Pathol* 168:357–363
454. Cavanagh JB (1958) On certain small tumours encountered in the temporal lobe. *Brain* 81:389–405
455. Cavanagh JB (1970) The proliferation of astrocytes around a needle wound in the rat's brain. *J Anat* 106:471–487
456. Cavanagh JB, Hopewell JW (1972) Mitotic activity in the subependymal plate of rats and the long-term consequences of X-irradiation. *J Neurol Sci* 15:471–482
457. Cavanagh JB, Lewis PD (1969) Perfusion-fixation, colchicine, and mitotic activity in the adult rat brain. *J Anat* 104:341–350
458. Cavenee WK, Dryja TP, Phillips RA, Benedict WF, Godbout R, Gallie BL, Murphree AL, Stong LC, White RL (1983) Expression of recessive alleles by chromosomal mechanisms in retinoblastoma. *Nature* 305:779–784
459. Cavenee WK, Hansen ME, Nordenskjöld M, Kock E, Maumenee I, Squire JA, Phillips RA, Gallie BL (1985) Genetic origin of mutations predisposing to retinoblastoma. *Science* 228:501–503
460. Cavenee WF (1980) Experimental observations: delayed necrosis in normal monkey brain. In: Gilbert HA, Kagan AR (eds) *Radiation damage to the nervous system*. Raven, New York, pp 1–38
461. Cavin LW, Dalrymple GV, McGuire EL, Maners AW, Broadwater JR (1990) CNS tumors induction by radiotherapy: a report of four new cases and estimate of dose required. *Int J Radiation Oncology Biol Phys* 18:399–406
462. Cawthon RM, Weiss R, Xu G, Viskochil D, Culver M, Stevens J, Robertson M, Dunn D, Gesteland R, O'Connell P, White R (1990) A major segment of the neurofibromatosis type 1 gene: cDNA sequence, genomic structure and point mutations. *Cell* 62:193–201
463. Celis JE, Celis A (1985) Cell cycle-dependent variations in the distribution of the nuclear protein cyclin proliferating cell nuclear antigen in cultured cells: subdivision of S phase. *Proc Natl Acad Sci USA* 82:3262–3266
464. Cerdà-Nicolas M, Kepes JJ (1993) Gliofibromas (including malignant forms), and gliosarcomas: a comparative study and review of the literature. *Acta Neuropathol (Berl)* 85:349–361
465. Cervós-Navarro J (1971) Elektronenmikroskopie der Hemangioblastome des ZNS und der angioblastischen Meningeome. *Acta Neuropathol (Berl)* 19:184–207
466. Cervós-Navarro J, Vasquez JJ (1969) An electron microscopic study of meningiomas. *Acta Neuropathol (Berl)* 13:301–323
467. Cervós-Navarro J, Matakas F, Lazaro MC (1968) Das Banprinrip Neurinoma. Ein Beitrag zur Histogenese der Nerventumoren. *Virchows Arch [A]* 345:276–291

468. Chadarévian JP de, Pattisapu JV, Faerber EN (1990) Desmoplastic cerebral astrocytoma of infancy. Light microscopy, immunohistochemistry and ultrastructure. *Cancer* 66:173–179
469. Chadderton RD, West CGH, Schulz S, Quirke DC, Gattamaneni R, Taylor R (1995) Radiotherapy in the treatment of low grade astrocytomas 2. The physical and cognitive sequelae. *Childs Nerv Syst* 11:443–448
470. Chaddock WM, Roycroft D, Brown MW (1983) Multicentric glioma as a cause of multiple cerebral lesion. *Neurosurgery* 13:170–175
471. Chaffee B, Donaghy RPM (1963) Meningioma of the fourth ventricle. Case report and technical note. *J Neurosurg* 20:520–522
472. Challa VR, Dixon MM, Marshall RB, Kelly DL Jr (1980) The vascular component in meningiomas associated with severe cerebral edema. *Neurosurgery* 7:363–368
473. Challa VR, Moody DM, Brown WR. (1995) Vascular malformations of the central nervous system. *J Neuropathol Exp Neurol* 54:609–621
474. Chamberlain MC (1994) Long survival in patients with acquired immune deficiency syndrome-related primary central nervous system lymphoma. *Cancer* 74:1728–1730
475. Chamberlain MC (1994) Gliomas in patients with acquired immune deficiency syndrome. *Cancer* 74:1912–1914
476. Chamberlain MC, Murovic J, Levin VA (1988) Absence of contrast enhancement on CT brain scans of patients with supratentorial malignant gliomas. *Neurology* 38:1371–1374
477. Chan PH, Fishman RA (1984) Phospholipid degradation and the early release of polyunsaturated fatty acids in the evolution of brain edema. In: Go KG, Baethmann A (eds) *Recent progress in the study and therapy of brain edema*. Plenum, New York pp 193–202
478. Chan PH, Schmidley JW, Fishmann RA, Longar SM (1984) Brain injury, edema and vascular permeability changes induced by oxygen-derived free radicals. *Neurology* 34:315–320
479. Chan RC, Thompson BG (1984) Morbidity, mortality, and quality of life following surgery for intracranial meningiomas. *J Neurosurg* 60:52–60
480. Chang CH, Horton J, Schoenfeld D, Salazar O, Perez-Ramayo R, Kramer S, Weinstein A, Nelson JS, Tsukada Y (1983) Comparison of postoperative radiotherapy and chemotherapy in the multidisciplinary management of malignant gliomas. *Cancer* 52:997–1007
481. Chason JL (1956) Subependymal mixed gliomas. *J Neuropathol Exp Neurol* 15:461–470
482. Chatty EM, Earle KM (1971) Medulloblastoma. A report of 201 cases with emphasis on the relationship of histologic variants to survival. *Cancer* 28:977–983
483. Chaudhry AP, Montes M, Cohn GA (1978) Ultrastructure of cerebellar hemangioblastoma. *Cancer* 42:1834–1850
484. Chauhan AN, Lewis PD (1979) A quantitative study of cell proliferation in ependyma and choroid plexus in the post-natal rat brain. *Neuropathol Appl Neurobiol* 5:303–309
485. Chauser B, Morris C, Field SB (1977) The effects of fast neutrons and X-rays on the subependymal layer of the rat brain. *Radiology* 122:821–823
486. Cheetham HD (1963) Experimental squamous metaplasia and squamous epithelioma formation in the pituitary of the rat. *Br J Cancer* 17:657–662
487. Chen F, Kshida T, Yao M, Hustand T, Glavac D, Dean M, Gnarr JR, Orcutt ML, Duh FM, Glenn G, Green J, Hsia YE, Lamiell J, Li H, Wei MH, Schmidt L, Tory K, Kuzmin I, Stackhouse T, Latif F, Linehan WM, Lerman MI, Zbar B (1995) Germ line mutations in the von Hippel-Lindau disease tumor suppressor gene: correlations with phenotype. *Hum Mut* 5:66–75
488. Chen P-L, Scully P, Shew J-Y, Wang JYJ, Lee W-H (1989) Phosphorylation of the retinoblastoma gene product is modulated during the cell cycle and cellular differentiation. *Cell* 58:1193–1198
489. Chen SC, Curran T, Morgan JI (1995) Apoptosis in the nervous system: new revelations. *J Clin Pathol* 48:7–12
490. Chen WYK, Liu HC (1990) Atypical (anaplastic) meningioma: relationship between histologic features and recurrence. A clinico-pathologic study. *Clin Neuropathol* 9:74–81
491. Chigasaki H (1963) Studies on the DNA synthesis function of glial cells by means of [3H]-thymidine microradioautography (Japanese). *Brain Nerve* (Tokyo) 15:767–781
492. Childhood Brain Tumor Consortium (1989) Intraobserver reproducibility in assigning brain tumors to classes in the World Health Organization diagnostic scheme. *J Neurooncol* 7:211–224

493. Chimelli L, Symon L, Scaravilli F (1984) Granular cell tumor of the fifth cranial nerve: further evidence for Schwann cell origin. *J Neuropathol Exp Neurol* 43:634–642
494. Chin HW, Hazel JJ, Kim TH, Webster JH (1980) Oligodendrogliomas. I. A clinical study of cerebral oligodendrogliomas. *Cancer* 45:1458–1466
495. Chin HW, Maruyama Y, Markesberry W, Young AB (1982) Intracranial ependymoma; results of radiotherapy at the University of Kentucky. *Cancer* 49:2276–2280
496. Chioventa M (1933) I gliomi dell'encefalo. Cappelli, Bologna
497. Cho ES, Connolly E, Porro RS (1974) Primary reticulum cell sarcoma of the brain in a renal transplantation recipient. Case report. *J Neurosurg* 41:235–239
498. Cho KG, Hoshino T, Nagashima T, Murovic JA, Wilson CB (1986) Prediction of tumor doubling time in recurrent meningiomas. Cell kinetics studies with bromodeoxyuridine labeling. *J Neurosurg* 65:790–794
499. Cho KG, Hoshino T, Pitts LH, Nomura K, Shimosato Y (1988) Proliferative potential of brain metastases. *Cancer* 62:512–515
500. Cho Y, Gorina S, Jeffrey PD, Pavletich NP (1994) Crystal structure of a p53 tumor suppressor-DNA complex: understanding tumorigenic mutations. *Science* 265:346–355
501. Choi BH (1986) Glial fibrillary acidic protein in radial glia of early human fetal cerebrum: a light and electron microscopic immunoperoxidase study. *J Neuropathol Exp Neurol* 45:408–418
502. Choi BH (1988) Developmental events during the early stages of cerebral cortex neurogenesis in man. A correlative light, electronmicroscopic, immunohistochemical and Golgi study. *Acta Neuropathol (Berl)* 75:441–447
503. Choi BH, Kim RC (1984) Expression of glial fibrillary acidic protein in immature oligodendroglia. *Science* 223:407–409
504. Choi BH, Lapham W (1978) Radial glia in the human foetal cerebrum: a combined Golgi, immunofluorescence and electronmicroscopy study. *Brain Res* 148:295–311
505. Choi BH, Lapham W (1983) Do radial glia give rise to both astroglial and oligodendroglial cells? *Develop Brain Res* 8:119–130
506. Choi NW, Schuman LM, Gullen WH (1970) Epidemiology of primary central nervous system neoplasms. II: case-control study. *Am J Epidemiol* 91:467–485
507. Choremis C, Economos D, Papadatos C, Gargoulas A (1956) Intraspinal epidermoid tumors (cholesteatomas) in patients treated for tuberculous meningitis. *Lancet* 271:437–439
508. Chou SM, Anderson JS (1991) Primary CNS malignant rhabdoid tumor (MRT): report of two cases and review of the literature. *Clin Neuropathol* 10:1–10
509. Chou TM, Chou SM (1989) Tuberous sclerosis in the premature infant: report of a case with immunohistochemistry in the CNS. *Clin Neuropathol* 8:45–52
510. Chouchair AL, Levin VA, Gutin PH, Davis RL, Silver P, Edwards MSB, Wilson CB (1986) Development of multiple lesions during radiation therapy and chemotherapy in patients with gliomas. *J Neurosurg* 65:654–658
511. Choux M, Lena G, Hassoun J (1983) Prognosis and long-term follow-up in patients with medulloblastoma. *Clin Neurosurg* 3:246–277
512. Choux M, Lena G, Genitori L (1991) Le craniopharyngiome de l'enfant. *Neurochirurgie (Paris)* 37 [Suppl 1]:12–165
513. Choux R, Hassoun J, Bernard M, Pellissier JM, Choux M, Toga M (1973) Ultrastructure d'un craniopharyngiome. Etude in vivo et in vitro. *Arch Anat Path* 21:179–188
514. Choux R, Hassoun J, Gambarelli D, Sedan R, Toga M (1975) Etude ultrastructurale d'un "méningiome humide" de Masson. *Bull Cancer* 62:125–136
515. Chowdhury C, Roy S, Mahapatra AK, Bhatia R (1985) Medullomyoblastoma. A teratoma. *Cancer* 55:1495–1500
516. Chozick BS, Weicker ME, Pezzullo JC, Jackson CL, Finkelstein SD, Ambler MW, Epstein MH, Finch PW (1994) Pattern of mutant p53 expression in human astrocytomas suggests the existence of alternate pathways of tumorigenesis. *Cancer* 73:406–415
517. Christensen D, Laursen H, Klinken L (1983) Prediction of recurrence in meningiomas after surgical treatment. *Acta Neuropathol (Berl)* 61:130–134
518. Christensen E (1937) Über Ganglionzellgeschwülste im Gehirn. *Virchows Arch [A]* 300:567–581
519. Christensen E, Lara DE (1953) Intracranial sarcomas. *J Neuropathol Exp Neurol* 12:41–56

520. Chung Chun HC, Schmidt-Ullrich RK, Wolfson A, Tercilla OE, Sagerman RH, King GA (1990) External beam radiotherapy for primary spinal cord tumors. *J Neurooncol* 9:211–217
521. Chung RY, Whaley J, Kley N, Anderson K, Louis DN, Menon A, Hettlich C, Freiman R, Hedley-Whyte ET, Martuza R, Jenkins R, Yandell D, Seizinger BR (1991) TP53 mutation and 17p deletion in human astrocytomas. *Genes Chrom Cancer* 3:323–331
522. Chusid JG (1948) Ependymoma in third and fourth ventricles with implants in spinal subarachnoid spaces. *Arch Neur Psych* 59:408–413
523. Ciric I, Ammirati M, Vick N, Mikhael M (1987) Supratentorial gliomas: surgical considerations and immediate postoperative results. Gross total resection versus partial resection. *Neurosurgery* 21:21–26
524. Claassen U, Kuntz G, Schmitt HP (1991) Malignant intracerebral granular cell tumor reacts positively with anti-alpha-1-antichymotrypsin and the MB2 antibody: a clue to the histogenesis of the brain granular cells? *Clin Neuropathol* 2:82–88
525. Claisse PJ, Lantos PL, Roscoe JP (1978) Analysis of N-ethyl-N-nitrosourea-induced brain carcinogenesis by sequential culturing during the latent period. II Morphology of the tumors induced by cell cultures. *J Natl Cancer Inst* 61:391–398
526. Clark GB, Henry JM, McKeever PE (1985) Cerebral pilocytic astrocytoma. *Cancer* 56:1128–1133
527. Clark WC, Bressler J (1988) Transforming growth factor activity in tumors of the central nervous system. *J Neurosurg* 68:920–924
528. Clark WC, Theofilos CS, Fleming JC (1989) Primary optic nerve sheath meningiomas. Report of nine cases. *J Neurosurg* 70:37–40
529. Clarke AR, Purdie CA, Harrison DJ, Morris RG, Bird CC, Hooper ML, Wyllie AH (1993) Thymocyte apoptosis induced by p53-dependent and independent pathways. *Nature* 362:849–852
530. Cleland J (1864) Description of two tumours adherent to the deep surface of the dura. *Glasgow Med J* 11:148–159
531. Clemmesen J (1965) Statistical studies in the etiology of malignant neoplasms. I. Review and results. *Acta Pathol Microbiol Scand [Suppl 174]* 422:538–542
532. Clendenon NR, Barth RF, Gordon WA, Goodman JH, Alam F, Staubus AE, Boesel CP, Yates AJ, Moeschberger ML, Fairchild RG, Kalef-Ezra JA (1990) Boron neutron capture therapy in a rat glioma. *Neurosurgery* 26:47–55
533. Clevenger CV, Epstein AL (1984) Identification of a nuclear protein component of interchromatin granules using a monoclonal antibody and immunogold electron microscopy. *Exp Cell Res* 151:194–207
534. Clevenger CV, Epstein AL, Bauer KD (1987) Modulation of the nuclear antigen p105 as a function of cell cycle progression. *J Cell Physiol* 130:336–343
535. Coakham HB (1986) Immunology of human brain tumors. *Eur J Cancer Clin Oncol* 20:145–149
536. Coakham HB, Lakshmi MS (1975) Tumour-associated surface antigen(s) in human astrocytomas. *Oncology* 31:233–243
537. Coakham HB, Garson JA, Allan PM, Harper EI, Brownell B, Kemshead JT, Lane EB (1985) Immunohistological diagnosis of central nervous system tumors using a monoclonal antibody panel. *J Clin Pathol* 38:165–173
538. Coakham HB, Garson JA, Allan PA (1985) Immunohistological diagnosis of central nervous system tumors using a monoclonal antibody panel. *J Clin Pathol* 38:165–173
539. Codegone ML, Peres B, Schiffer D (1970) Caratterizzazione istochimica dei lipidi e loro significato nel neurinoma. *Acta Neurol (Napoli)* 25:184–187
540. Coffin CM, Mukai K, Dehner LP (1983) Glial differentiation in medulloblastomas: histogenic insight, glial reaction, or invasion of brain? *Am J Surg Pathol* 7:555–565
541. Coffin CM, Wick MR, Braun JT, Dehner LP (1986) Choroid plexus neoplasms: clinicopathologic and immunohistochemical studies. *Am J Surg Pathol* 10:394–404
542. Coffin CM, Braun JT, Wick MR, Dehner LP (1990) A clinicopathologic and immunohistochemical analysis of 53 cases of medulloblastoma with emphasis on synaptophysin expression. *Modern Pathol* 2:164–170
543. Cohadon F (1987) Physiopathologie des oedèmes cérébraux. *Rev Neurol* 143:3–20
544. Cohadon F, Aoua D, Rougier A, Vital C, Rivel J, Dartigues JF (1985) Histologic and nonhistologic factors correlated with survival time in supratentorial astrocytic tumors. *J Neuro-oncol* 3:105–111

545. Cohen A, Modan B (1968) Some epidemiologic aspects of neoplastic diseases in Israeli immigrant population. III. Brain tumors. *Cancer*, 22:1323–1328
546. Cohén AM, Hay ED (1971) Secretion of collagen by embryonic neuroepithelium at the time of spinal cord-somite interaction. *Dev Biol* 26:578–605
547. Cohen ME, Duffner PK (1984) Brain tumors in children. Principles of diagnosis and treatment. International review of child Neurology, Raven, New York, pp 193–210
548. Cohnheim J (1878) Vorlesungen über allgemeine Pathologie. Hirschwald, Berlin
549. Coia LR, Aaronson N, Linggood, Loeffler J, Priestman TJ (1992) A report of the consensus workshop panel on the treatment of brain metastases. *Int J Radiat Oncol Biol Phys* 23:223–227
550. Coleman MJ, Tonkin J, Bleasel K, Lim GHK (1972) Glomus jugulare tumour: a case report. *Aust NZJ Surg* 42:64–68
551. Coley BL (1949) Neoplasms of bone. Noeher, New York
552. Collins PV, James DC (1990) Molecular genetics of primary intracranial tumors. *Curr Opin Oncol* 2:666–672
553. Collins VP, Loeffler RK, Tivey H (1956) Observations on growth rates of human tumors. *Am J Roentgen* 76:988–1000
554. Colombo F (1989) Linear accelerator radiosurgery of cerebral gliomas. In: Broggi G, Gerosa MA (eds) Cerebral gliomas. Elsevier, Amsterdam, pp 221–225
555. Concha S, Hamilton BPM, Millan JC, McQueen D (1975) Symptomatic Rathke's cleft cyst with amyloid stroma. *J Neurol Neurosurg Psychiatry* 38:782–786
556. Conley FK (1979) The immunohistochemical localization of GFAP protein in experimental murine CNS tumors. *Acta Neuropathol (Berl)* 45:9–16
557. Conley FK, Rubinstein LJ, Spence AM (1976) Studies on experimental malignant nerve sheath tumors maintained in tissue and organ culture systems II. Electron microscopy observations. *Acta Neuropathol (Berl)* 34:293–310
558. Constine LS, Konski A, Ekholm S, McDonald S, Rubin P (1988) Adverse effects of brain irradiation correlated with MR and CT imaging. *Int J Radiat Oncol Biol Phys* 15:319–330
559. Cook RD, Wisniewski HM (1973) The role of oligodendroglia and astroglia in Wallerian degeneration of the optic nerve. *Brain Res* 61:191–206
560. Coomber BD, Steward PA, Hayakawa E, Farrell CL, Del Maestro RF (1987) Quantitative morphology of human glioblastoma multiforme microvessels: structural basis of blood brain barrier defect. *J Neurooncol* 5:299–307
561. Cooney LM Jr, Solitare GB (1972) Primary intracranial tumors in the elderly. *Geriatrics* 27:94–104
562. Coons SW, Johnson PC (1993) Regional heterogeneity in the proliferative activity of human gliomas as measured by the Ki 67 labeling index. *J Neuropathol Exp Neurol* 52:609–618
563. Coons SW, Davis JR, Way DL (1988) Correlation of DNA and histology in prognosis of astrocytomas. *Am J Clin Pathol* 90:289–293
564. Coons SW, Johnson PC, Shapiro JR (1995) Cytogenetic and flow cytometry DNA analysis of regional heterogeneity in low grade human glioma. *Cancer Res* 55:1569–1577
565. Cooper C, Jones HG, Weller RO, Walker V (1984) Production of prostaglandins and thromboxane by isolated cells from intracranial tumors. *J Neurol Neurosurg Psychiatry* 47:579–584
566. Cooper JA, Whyte P (1989) RB and the cell cycle: entrance or exit? *Cell* 58:1109–1011
567. Cooper PR, Epstein F (1985) Radical resection of intramedullary spinal cord tumors in adults. *J Neurosurg* 63:492–499
568. Copeland DD, Bigner DD, Vogel FS (1975) The induction of intracranial neoplasms by the inoculation of Avian Sarcoma virus in perinatal and adult rats. *J Neuropathol Exp Neurol* 34:340–358
569. Copeland DD, Bell SW, Shelburne JD (1978) Hemidesmosome-like intercellular specializations in human meningioma. *Cancer* 41:2242–2249
570. Coppeto JR, Roberts M (1979) Fibrosarcoma after proton-beam pituitary ablation. *Arch Neurol* 36:380–381
571. Corallini A, Barbanti-Brodano G, Bortoloni W, Nenci I, Cassai E, Tampieri H, Portolani M, Borgatti M (1977) High incidence of ependymomas induced by BK virus a human papovavirus: brief communication. *J Natl Cancer Inst* 59:1561–1564
572. Cordera S, Cavalla P, Soffietti R, Giordana MT (1995) Solitary cerebral metastasis: a challenge for the neuropathologist. *Ital J Neurol Sci* 6:406



573. Cordier S, Iglesias MJ, Le Goarter C, Guyot MM, Mandereau L, Heman D (1994). Incidence and risk factors for childhood brain tumors in the Ile de France. *Int J Cancer* 59:776-782
574. Cornford EM, Hyman S, Black KL, Cornford ME, Vinters HU, Pardridge WM (1995) High expression of the Glut 1 glucose transporter in human brain hemangioblastoma endothelium. *J Neuropathol Exp Neurol* 54:842-851
575. Cornil MM, Paillas JE, Badier M (1951) Sur les récides malignes des gliomes bénins. *Rev Neurol* 7:494-499
576. Cossa MMP, Duplay J, Martin P (1951) A propòs d'une observation de méningiomas multiples. *Rev Neurol* 85:552-553
577. Costero I, Pomerat CM, Jackson IJ, Barroso-Moguel R, Chevez A (1955) Tumors of the human nervous system in tissue culture. I. The cultivation and cytology of meningioma cells. *J Natl Cancer Inst* 15:1319-1339
578. Costero I, Pomerat CM, Barroso-Moguel R, Chevez A (1955) Tumors of the human system in tissue culture. II. An analysis of fibroblastic activity in meningiomas. *J Natl Cancer Inst* 15:1341-1365
579. Costero I, Barroso-Moguel R, Chevez A (1962) Aspects of the pathology of the chemoreceptors in the carotid body tumors. *Proceedings of the IVth International Congress on Neuro-pathology*, vol 2. Thieme, Stuttgart, p 217
580. Cotter TG, Lennon SV, Glynn JG, Martin SJ (1990) Cell death via apoptosis and its relationship to growth: development and differentiation of both tumour and normal cell. *Anticancer Res* 10:1153-1160
- 580a. Couldwell WT, Hinton DR (1995) Oligodendroglioma. In: *Brain Tumors*, Kaye AH, Laws ER Jr (eds) Churchill Livingstone, New York, pp 479-491
581. Coulon RA, Till K (1977) Intracranial ependymomas in children. A review of 43 cases. *Childs Brain* 3:154-168
582. Courville CB (1936) Multiple primary tumors of the brain. Review of the literature and report of twenty-one cases. *Am J Cancer* 26:703-731
583. Couturier J, Delattre O, Kujas M, Philippon J, Peter M, Rouleau G, Aurias A, Thomas G (1990) Assessment of chromosome 22 anomalies in neurinomas by karyotype and RFLP analyses. *Cancer Genet Cytogenet* 45:55-62
584. Cowie TN (1953) Two tumours within a fractured skull. *Br J Radiol* 26:265-266
585. Cox JD, Yesner RA (1979) Adenocarcinoma of the lung: recent results from the Veterans Administration Lung Group. *Am Rev Resp Dis* 120:1025-1031
586. Cox LB (1933) The cytology of glioma group; with special reference to the inclusion of cells derived from the invaded tissue. *Am J Pathol* 9:839-898
587. Coxe WS, Luse SA (1964) Colloid cysts of third ventricle. An electron microscopic study. *J Neuropathol Exp Neurol* 23:431-445
588. Craig JM (1949) Encephalo-trigeminal angiomatosis (Sturge-Weber's disease). *J Neuropathol Exp Neurol* 8:305-318
589. Craig W, Keith HM, Kernohan JW (1949) Tumors of the brain occurring in childhood. *Acta Psych Neurol Scand* 24:375-390
590. Cravioto H (1969) The ultrastructure of acoustic nerve tumors. *Acta Neuropathol (Berl)* 12:116-140
591. Cravioto H, Dart D (1973) The ultrastructure of "pinealoma" (seminoma-like tumor of the pineal region). *J Neuropathol Exp Neurol* 32:552-565
592. Cravioto H, Lockwood R (1969) The behavior of acoustic neuroma in tissue culture. *Acta Neuropathol (Berl)* 12:141-157
593. Cravioto H, Palekar L, Weiss E, Bennet K (1972) Experimental neurinoma in tissue culture. *Acta Neuropathol (Berl)* 21:154-164
594. Cravioto H, Weiss JF, Weiss E, Goebel HH, Ransohoff J (1973) Biological characteristics of peripheral nerve tumors induced with ethylnitrosourea. *Acta Neuropathol (Berl)* 23:265-280
595. Cravioto H, Hirt P, Bloom A, Dunovsky F (1976) Immunology of experimental brain tumors in inbred rats. *J Neuropathol Exp Neurol* 35:356
596. Crawford J, Rubinstein LJ, Russell D (1958) Follow-up of cerebellar astrocytomas in relation to their pathology. *J Neurol Neurosurg Psychiatry* 21:64-72

597. Criscuolo GR, Merrill MJ, Oldfield EH (1988) Further characterization of malignant glioma-derived vascular permeability factor. *J Neurosurg* 69:254–262
598. Critchley M, Ironside RN (1926) The pituitary adamantinomatoma. *Brain* 49:437–481
599. Crocker J, Jones EL, Curran RC (1982) A quantitative study of a-naphthylacetate esterase-positive cells in non-Hodgkin's lymphomas and reactive lymphonodes. *J Clin Pathol* 35:1066–1068
600. Crompton MR, Gautier-Smith PC (1970) The prediction of recurrence in meningiomas. *J Neurol Neurosurg Psychiatry* 33:80–87
601. Crompton MR, Layton DD (1961) Delayed radionecrosis of the brain following therapeutic X-radiation of the pituitary. *Brain* 84:85–101
602. Crone KR, Challa VR, Kute TE, Moody DM, Kelly DL Jr. (1988) Relationship between flow cytometric features and clinical behavior of meningiomas. *Neurosurgery* 23:720–724
603. Crosato F (1957) Contributo allo studio delle fibre di Rosenthal. *Giorn Psich Neuropathol* 1:107–122
604. Cross KR, Cooper TJ (1952) Intracranial neoplasms with extracranial metastases. Report of two cases. *J Neuropathol Exp Neurol* 11:200–208
605. Cross M, Dexter M (1991) Growth factors in development, transformation, and tumorigenesis. *Cell* 64:271–280
- 605a. Crossen JR, Garwood D, Glatstein E, Neuwelt EA (1994) Neurobehavioral sequelae of cranial irradiation in adults - A review of radiation-induced encephalopathy. *J Clin Oncol* 12:3
606. Crossey PA, Richards FM, Foster K, Green JS, Prowse A, Latf F, Lerman MI, Zbar B, Nabeel AA, Ferguson-Smith A, Maher ER, (1994) Identification of intragenic mutations in the von Hippel-Lindau disease tumor suppressor gene and correlation with disease phenotype. *Hum Mol Genet* 8:1303–1308
607. Crouse SK, Berg BO (1972) Intracranial meningiomas in childhood and adolescence. *Neurology* 22:135–141
608. Crowell RM, Wepsic JG (1972) Thoracic cord compression due to chondrosarcoma in two cousins with hereditary exostoses. Report of two cases. *J Neurosurg* 36:86–89
609. Cruveilhier J (1829) *Anatomie pathologique du corps humain*. Baillière, Paris
610. Cruveilhier J (1835) *Anatomie pathologique du corps humain*, vol 8. Baillière, Paris, pp 1829–1835
611. Cruz-Sanchez FF, Cervós-Navarro J, Kashiara M, Ferszt R (1987) Intracerebral neurinomas in a case of von Recklinghausen's disease (neurofibromatosis). *Clin Neuropathol* 6:174–178
612. Cruz-Sanchez FF, Austein J, Rossi ML, Cervós-Navarro J, Hughues JT (1989) Ependymoblastoma; a histological, immunohistochemical and ultrastructural study of five cases. *Histopathology* 12:17–27
613. Cruz-Sanchez FF, Rossi ML, Hughes JT, Esiri MM, Coakham HB (1989) Medulloblastoma. An immunohistological study of 50 cases. *Acta Neuropathol (Berl)* 79:205–210
614. Cruz-Sanchez FF, Rossi ML, Hughes JT, Moss TM (1991) Differentiation in embryonal neuroepithelial tumors of the central nervous system. *Cancer* 67:965–967
615. Csanda E (1980) Radiation brain edema. *Adv Neurol* 28:125–146
616. Culler FL, James HE, Simon ML, Lee Jones K (1985) Identification of gonadotropin-releasing hormone in neurons of a hypothalamic hamartoma in a boy with precocious puberty. *Neurosurgery* 17:408–412
617. Culver KW, Ram Z, Wallbridge S, Ishii H, Oldfield EH, Blaese RM (1992) In vivo gene transfer with retroviral vector-producer cells for treatment of experimental brain tumors. *Science* 256:1550–1552
618. Cuneo HM, Rand CW (1952) Brain tumors of childhood. Thomas, Springfield, pp 116–125
619. Curatolo P, Cusmai R, Finocchi G, Boscherini B (1984) Gelastic epilepsy and true precocious puberty due to hypothalamic hamartoma. *Dev Med Child Neurol* 26:509–514
620. Curnes JT, Laster DW, Ball MR (1986) Magnetic resonance imaging of radiation injury to the brain. *AJNR* 7:389–394
621. Curran WJ, Scott CB, Show EG, Nelson JS (1995) Radiation therapy oncology group (RTOG) Clinical trials for brain tumor patients: update 1995. In: 11th International Conference on Brain Tumor Research and Therapy, 31 October–3 November 1995, Silverado, Ca (abstr)
622. Currie S, Urich H (1974) Concurrence of multiple sclerosis and glioma. *J Neurol Neurosurg Psychiatry* 37:598–605

623. Cushing H (1922) The meningeomas (dural endotheliomas). Their source and favorite seats of origin (Cavendish lecture). *Brain* 45:282–316
624. Cushing H (1930) Experience with the cerebellar medulloblastomas. *Acta Pathol Microbiol Scand* 7:1–86
625. Cushing H (1931) Experiences with the cerebellar astrocytomas. *Surg Gyn Obstetr* 52:129–204
626. Cushing H (1932) Intracranial tumours. Notes upon a series of two thousand verified cases with surgical-mortality percentages pertaining thereto. Thomas, Springfield, pp 93–98
627. Cushing H (1935) *Intrakranielle Tumoren*. Springer, Berlin
628. Cushing H, Bailey P (1928) Tumours arising from the blood-vessels of the brain. Angiomatous malformations and hemangioblastomas. Thomas, Springfield
629. Cushing H, Eisenhardt L (1938) Meningiomas, their classification, regional behaviour, life history and surgical results. Thomas, Springfield
630. Cushing H, Weed LH (1915) Studies on the cerebrospinal fluid and its pathway. IX. Calcareous and osseous deposits in the arachnoidea. *Bull J Hopkins Hosp* 26:367–380
631. D'Alessandro G, Di Giovanni M, Jannuzzi L, Guidetti E, Bottacchi E (1995) Epidemiology of primary intracranial tumors in the Valle d'Aosta (Italy) during the 6-year period 1986–1991. *Neuroepidemiology* 14:139–146
632. D'Andrea AD, Packer RJ, Rorke LB, Bilaniuk LT, Sutton LN, Bruce, DA, Schut L (1987) Pineocytomas of childhood: a reappraisal of natural history and response to therapy. *Cancer* 59:1353–1357
633. D'Andrea F, De Divitiis E (1966) Neoplasie metastatiche dell'encefalo. Laux, Naples
634. D'Ardenne AJ, Kirkpatrick P, Sykes BC (1984) Distribution of laminin, fibronectin and interstitial collagen type III in soft tissue tumors. *J Clin Pathol* 37:815–904
635. Dahl D (1981) The Vimentin-GFAP protein transition in rat neuroglia cytoskeleton occurs at the time of myelination. *J Neurosci Res* 6:741–748
636. Dahl D, Bignami A (1973) Glial fibrillary acidic protein from normal human brain, purification and properties. *Brain Res* 57:343–360
637. Dahl D, Bignami A, Weber K, Osborn M (1981) Filament proteins in rat optic nerves undergoing wallerian degeneration; localization of vimentin, the fibroblastic 100 A filament protein, in normal and reactive astrocytes. *Exp Neurol* 13:496–506
638. Dahl D, Rueger DC, Bignami A (1981) Vimentin, the 57.000 molecular weight protein of fibroblast filaments, is the major cytoskeletal component in immature glia. *Eur J Cell Biol* 24:191–196
639. Dahl D, Choi NH, Miles L, Nguyen BT, Bignami A (1982) Glial fibrillary acidic (GFA) protein immunohistochemistry in neurooncology: a progress report. *Pathol Res Pract* 168:374–394
640. Dahl HA (1963) Fine structure of cilia in rat cerebral cortex. *Zellforsch* 60:369–376
641. Dahl O (1980) Effects of hyperthermia on a neurogenic rat cell line (BT<sub>4</sub>C) in culture. Development of thermal tolerance during continuous heating. *Acta Radiol Oncol* 19:489–496
642. Dahlin DC (1967) Bone tumors. General aspects and data on 3987 cases, 2nd edn. Thomas, Springfield
643. Daita G, Yonemasu Y, Muraoka S, Nakai H, Maeda T (1991) A case anaplastic astrocytoma transformed from pleomorphic xanthoastrocytoma. *Brain Tumor Pathol* 8:63–66
644. Daly MB, Swift M (1978) Epidemiological factors related to the malignant neoplasms in ataxia-telegenectasia. *J Chronic Dis* 31:625–634
645. Dandy WE (1937) Carotid-cavernosus aneurysms. *Zbl Neurochir* 2:165–206
646. Dardick I, Hammar SP, Scheithauer BW (1989) Ultrastructural spectrum of hemangiopericytoma: a comparative study of fetal, adult and neoplastic pericytes. *Ultrastruct Pathol* 13:111–154
647. Darling JL, Bradford L, Koppel H, Martin JM, Pilkington GJ, Lantos PL, Thomas DGT (1986) The relationship between cell biological characteristics and drug sensitivity in 6 clonal lines derived from a spontaneous murine astrocytoma. *Br J Cancer* 54:177
648. Das GD (1979) Gliogenesis and ependymogenesis during embryonic development of the rat. *J Neurol Sci* 43:193–204
649. Dastur DK (1982) Cerebral ganglioglioblastoma: an unusual brain tumor of the neuron series. *J Neurol Neurosurg Psychiatry* 45:139–142
650. Dastur DK, Lalitha VS (1970) Pathological analysis of intracranial space-occupying lesions in 1000 cases including children. Part 3. Vascular tumours and hamartomas; meningiomas; schwannomas. *J Neurol Sci* 11:501–535

651. Daum S, Foncin JF (1963) Les tumeurs diffuses des leptoméniges. *Rev Neurol* 108:597–612
652. Daumas-Duport C (1989) A new uniform grading system (using Mayo Clinic material). In: Fields WS (ed) *Primary brain tumors. A review of histologic classification*. Springer, Berlin Heidelberg New York, pp 159–170
653. Daumas-Duport C (1993) Dysembryoplastic neuroepithelial tumours. *Brain Pathol* 3:283–295
654. Daumas-Duport C, Scheithauer BW, Kelly PJ (1987) A histologic and cytologic method for the spatial definition of gliomas. *Mayo Clin Proc* 62:435–449
655. Daumas-Duport C, Scheithauer B, O'Fallon J, Kelly P (1988) Grading of astrocytomas. A simple and reproducible method. *Cancer* 62:2152–2165
656. Daumas-Duport C, Scheithauer BW, Chodkiewicz JP, Laws E, Vedrenne C (1988) Dysembryoplastic neuroepithelial tumor: a surgically curable tumor of young patients with intractable partial seizures. *Neurosurgery* 23:545–556
657. Davidson GS, Hope JK (1989) Meningeal tumors of childhood. *Cancer* 63:1205–1210
658. Davis C, Barnard RO (1985) Malignant behavior of myxopapillary ependymoma: report of three cases. *J Neurosurg* 62:925–929
659. Davis C, Joglekar B (1981) Cerebellar astrocytomas in children and young adults. *J Neurol Neurosurg Psychiatry* 44:820–828
660. Davis LR, Martin J, Padberg J, Anderson RK (1950) A study of 182 patients with verified astrocytoma, astroblastoma and oligodendroglioma of the brain. *J Neurosurg* 7:299–312
661. Davis LW (1989) Presidential address: Malignant glioma. A nemesis which requires clinical and basic investigation in radiation oncology. *Int J Radiat Oncol Biol Phys* 16:1355–1365
662. Davis RL (1971) Astrocytomas. In: Minckler J (ed) *Pathology of the nervous system*, vol 2. McGraw-Hill, New York, pp 2007–2025
663. Davis RL (1989) Grading of glioma. In: Fields WS (ed) *Primary brain tumors. A review of histologic classification*. Springer, Berlin Heidelberg New York, pp 150–158
664. Davis RL, Barger GR, Gutin PH, Phillips ThL (1984) Response of human malignant gliomas and CNS tissue to  $^{125}\text{I}$  brachytherapy: a study of seven autopsy cases. *Acta Neurochir (Wien)* 33:301–305
665. Davis RL, Onda K, Shubuya M, Lamborn K, Hoshino T (1995). Proliferation markers in gliomas: a comparison of BUDR, Ki-67, and MIB.1. *J Neurooncol* 1:9–12
666. Davison AM, Curnez ML, Banik HL, Oxberry J (1966) Myelinogenesis in the rat brain. *Nature* 212:1373–1374
667. De Armond SJ, Eng LF (1984) Immunohistochemistry: techniques and application to neurooncology. In: Rosenblum ML, Wilson CB (eds) *Brain tumor biology*. *Progr Exp Rumor Res* 27:92–117
668. De Armond SJ, Eng LF, Rubinstein LJ (1980) The application of glial fibrillary acidic (GFA) protein immunohistochemistry in neurooncology. A progress report. *Pathol Res Pract* 168:374–394
669. De Carli A, La Vecchia C (1984) Cancer mortality in Italy, 1955–1978. *Tumori [Suppl]* 70:581–742
670. De Caro R, Giordano R, Parenti A, Zuccarello M (1982) Osteomatous meningioma. Report of two cases. *Acta Neurochir* 60:313–317
671. De Chadarevian JP, Guyda HJ, Hollemberg RD (1984) Hypothalamic polar spongioblastoma associated with the diencephalic syndrome: ultrastructural demonstration of a neuro-endocrine organization. *Virchows Arch [A]* 402:465–474
672. De Clerk YA, Shimada H, Gonzales-Gomez I, Raffel C (1994) Tumoral invasion in the central nervous system. *J Neurooncol* 18:111–121
673. De la Monte SM (1989) Uniform lineage of oligodendroglioma. *Am J Pathol* 135:529–540
674. De Leon GA, Zaeri N, Foley CM (1988) Olfactory hamartomas in tuberous sclerosis. *J Neurol Sci* 87:187–194
675. De Martin R, Haendler B, Hofer-Warbinek R, Gangitsch H, Wrann M, Schlusener H, Seifert JM, Bodmer S, Fontana A, Hofer E (1987) Complementary DNA for human glioblastoma-derived T cell suppressor factor, a novel member of the transforming growth factor-B gene family. *EMBO J* 6:3673–3677
676. De Mascarel A, Vital C, Rivel J, Deminiere C, Trojani M, De Mascarel I, Sakiri S (1983) Lymphomes malins non hodgkiniens primitifs du cerveau. Etude anatomoclinique et immunopathologique de vingt et un cas. *Semin Hop Paris* 59:179–184

677. De Michele DJ, Di Chiro G (1991) Grading meningiomas by positron emission tomography. In: Al-Mefty O (ed) *Meningiomas*. Raven, New York, pp 243–253
678. De Morsier G (1962) Les kystes épendymaires colloïdes du septum pellucidum et des ventricules latéraux. *Schwz Arch Neurol Neurochir Physchiatr* 90:34–56
679. De Pablo F, De la Rosa EJ (1995) The developing CNS: a scenario for the action of proinsulin, insulin and insulin-like growth factors. *TINS* 3:143–150
680. De Reuck J, Vander Hecken H (1975) The anatomy of the late radiation encephalopathy. *Eur Neurol* 13:481–494
681. De Ridder L, Laerum OD (1981) Invasion of rat neurogenic cell lines in embryonic chick heart fragments in vitro. *J Natl Cancer Inst* 66:723–728
682. De Tribolet N (1989) Immunology of gliomas. *Childs Nerv Syst* 5:60–65
683. De Tribolet N, Carrel S, Mach JP (1984) Brain tumor-associated antigens. In: Rosenblum ML, Wilson CB (eds) *Brain tumor biology*. *Prog Exp Tumor Res* 27:118–131
684. De Vitry F, Picart R, Jaque C, Tixier-Vidal A (1981) Glial fibrillary acidic protein. A cellular marker of tanyocytes in the mouse hypothalamus. *Develop Neurosci* 4:457–460
685. Deane BR, Lantos PL (1981) The vasculature of experimental brain tumors. 1. A sequential light and electron microscope study of angiogenesis. *J Neurol Sci* 49:55–66
686. Deane BR, Lantos PL (1981) The vasculature of experimental brain tumors. 2. A quantitative assessment of morphological abnormalities. *J Neurol Sci* 49:67–77
687. DeAngelis LM (1991) Primary central nervous system lymphoma: a new clinical challenge. *Neurology* 41:619–621
688. DeAngelis LM, Mandell LR, Thaler HT, Kimmel DW, Galicich JH, Fuks Z, Posner JB (1989) The role of postoperative radiotherapy after resection of single brain metastases. *Neurosurgery* 25:798–805
689. DeAngelis LM, Delattre JY, Posner J (1989) Radiation-induced dementia in patients cured of brain metastases. *Neurology* 39:789–796
690. DeAngelis LM, Yahalom J, Heinemann M-H, Cirrincione C, Thaler HT, Krol G (1990) Primary CNS lymphoma: combined treatment with chemotherapy and radiotherapy. *Neurology* 40:80–86
691. Deck JHN, Rubinstein LJ (1981) Glial fibrillary acidic protein in stromal cells of some capillary hemangioblastomas: significance and possible implications of an immunoperoxidase study. *Acta Neuropathol (Berl)* 54:173–181
692. Deck JHN, Eng L, Bigbee J, Woodcock SM (1978) The role of glial fibrillary acidic protein in the diagnosis of central nervous system tumors. *Acta Neuropathol (Berl)* 42:183–190
693. Deck MDF (1980) Imaging techniques in the diagnosis of radiation damage to the central nervous system. In: Gilbert HA, Kagan AR (eds) *Radiation damage to the nervous system*. Raven, New York, pp 107–127
694. Decker RE (1985) The ectopic pituitary gland in cases of craniopharyngioma. Report of two cases. *J Neurosurg* 62:291–292
695. Deckert M, Reifenberger G, Wechsler W (1989) Determination of the proliferative potential of human brain tumors using monoclonal antibody Ki-67. *J Cancer Res Clin Oncol* 115:179–188
696. Dedhar S (1990) Integrins and tumor invasion. *Bioessays* 12:583–590
697. Deen DF, Tofilon (1984) Combined effects of drugs and radiation against tumor cells. *Prog Exp Tumor Res* 28:183–197
698. Deen DF, Williams ME, Wheeler KT (1979) Comparison of the CCNU and BCNU modification of the in vitro radiation response in 9L brain tumor cells of rats. *Int J Radiat Oncol Biol Phys* 5:1541–1548
699. Deen HG, Laws ER (1981) Multiple primary brain tumours of different cell types. *Neurosurgery* 8:20–25
700. DeGirolami U, Zvaigzne O (1973) Modification of the Achúcarro-Hortega pineal stain for paraffin-embedded formalin-fixed tissue. *Stain Technol* 48:48–50
701. Deiters O (1865) *Untersuchungen über Gehirn und Rückenmark des Menschen und der Säugetiere*. Vieweg, Braunschweig
702. DeJong AS, Van Mark M, Albus-Lutter CE, Van Raamsdonk W, Voute PA (1984) Myosin and myoglobin as tumor markers in the diagnosis of rhabdomyosarcoma: a comparative study. *Am J Surg Pathol* 8:521–528

703. del Arco A, Garcia J, Arribas C, Barrio R, Blazquez MG, Izquierdo JM (1993) Timing of p53 mutations during astrocytoma tumorigenesis. *Hum Mol Genet* 2:1687-1690
704. Del Cerro MA, Snider RS (1972) Studies on the developing cerebellum II. The ultrastructure of the external granular layer. *J Comp Neurol* 144:131-138
705. Del Maestro R, Megyesi JF, Farrell CL (1990) Mechanisms of tumor-associated edema: a review. *Can J Neurol Sci* 17:177-183
706. Delattre JY, Poisson M (1990) Complications neurologiques de la radiothérapie cérébrale: apport des études expérimentales. *Bull Cancer* 77:715-724
707. Delattre JY, Krol G, Thaler HT, Posner JB (1988) Distribution of brain metastases. *Arch Neurol* 45:741-744
708. Delattre JY, Rosenblum MK, Thaler HT, Mandell L, Shapiro WR, Posner JB (1988) A model of radiation myelopathy in the rat. Pathology, regional capillary permeability changes and treatment with dexamethasone. *Brain* 111:1319-1336
709. Delattre JY, Shapiro WR, Posner JB (1989) Acute effects of low-dose cranial irradiation on regional capillary permeability in experimental brain tumor. *J Neurol Sci* 90:147-153
710. Delpach A, Delpach B, Girard N, Vidard MN (1978) Localization immunohistologique des 3 antigènes associés au tissu nerveux (GFA, ANS, brain glycoprotein). *Biol Cell* 32:207-214
711. Denekamp J, Fowler JF (1977) Cell proliferation kinetics and radiation therapy. In: Becker FE (ed) *Cancer - a comprehensive treatise*. Plenum, New York, pp 101-107
712. Derenzini M, Betts CM, Ceccarelli C, Eusebi V (1986) Ultrastructural organization of nucleoli in benign nevi and malignant melanomas. *Virchows Arch [B]* 52:343-352
713. Derome PJ, Visot A (1991) Bony reaction and invasion in meningiomas. In: Al-Mefty O (ed) *Meningiomas*. Raven, New York, pp 169-180
714. Deruaz JP, Janzer RC, Costa J (1993) Cellular Schwannomas of the intracranial and intraspinal compartment: morphological and immunological characteristics compared with classical benign Schwannomas. *J Neuropathol Exp Neurol* 52:114-118
715. Deutch M, Rewers AB, Redgate ES, Fisher ER, Boggs SS (1990) Intra-cerebral ventricular infusion of 5-iodo-2-deoxyuridine (IUDR) as a radiosensitizer in the treatment of a rat glioma. *Int J Radiat Oncol Biol Phys* 19:85-87
716. Deutsch M, Green SB, Strike TA, Burger PC, Robertson JT, Selker RG, Shapiro WR, Mealey JR, Ransohoff J, Paoletti P, Smith KR, Odom GL, Hunt WE, Young B, Alexander E, Walker MD, Pistenmaa DA (1989) Results of randomized trial comparing BCNU plus radiotherapy, streptozotocin plus radiotherapy, and BCNU following misonidazole plus radiotherapy in the postoperative treatment of malignant glioma. *Int J Radiat Oncol Biol Phys* 16:1389-1396
717. Dewey WC, Holahan EV (1984) Hyperthermia - basic biology. *Prog Exp Tumor Res* 28:198-219
718. Di Carlo EF, Amberson JB, Matrokac CE, Ballard P, Moore A, Mouradian JA (1986) Malignant lymphomas and the acquired immunodeficiency syndrome: evaluation of 30 cases using a working formulation. *Arch Pathol Lab Med* 110:1012-1016
719. Di Chiro G, Brooks RA, Patronas NJ, Bairamian D, Kornblith PL, Smith BH, Mansi L, Barker J (1984) Issues in the "in vivo" measurement of glucose metabolism of human central nervous system tumors. *Ann Neurol [Suppl]* 15:5138-5146
720. Di Chiro G, Oldfield E, Wright DC, De Michele D, Katz DA, Patronas NJ, Doppman JL, Larson SM, Ito M, Kufta C (1987) Cerebral necrosis after radiotherapy and/or intrarterial chemotherapy for brain tumors: PET and neuropathologic studies. *AJNR* 8:1083-1091
721. Di Cunto F, Di Sapio A, Zappador C, Mauro A, Schiffer D (1995) Human gliomas express HOX genes. *Neuropathol Appl Neurobiol* 21 [Suppl 1]:41
722. Di Lorenzo N, Nolletti A, Palma L (1978) Late cerebral radionecrosis. *Surg Neurol* 10:281-290
723. Di Paolo DP, Zimmerman RA, Rorke LB, Zackai EH, Bilaniuk LT, Yachnis AT (1995) Neurofibromatosis type 1: pathologic substrate of high signal - intensity foci in the brain. *Radiology* 195:721-724
724. Di Rocco C, Iannelli A, Ceddia A (1991) Intracranial tumors of the first year of life. A cooperative survey of the 1986-1987 education committee of the ISPN. *Childs Nerv Syst* 7:150-153
725. Dick SJ, Macchi B, Papazoglou S, Oldfield EM, Kornblith PL, Smith BH, Gately MV (1983) Lymphoid cell-glioma cell interaction enhances cell coat production by human gliomas: novel suppressor mechanism. *Science* 220:739-742
726. Dickson DW, Hart MN, Menezes A, Cancilla PA (1983) Medulloblastoma with glial and rhabdomyoblastic differentiation. *J Neuropathol Exp Neurol* 42:639-647

727. Dickson DW, Suzuki KI, Kanner R, Weitz S, Horoupian DS (1986) Cerebral granular cell tumor: immunohistochemical and electron microscopic study. *J Neuropathol Exp Neurol* 45:304–314
728. Diedrich U, Eckermann O, Schmidtke J (1988) Rare Ha-ras and c-mos alleles in patients with intracranial tumors. *Neurology* 38:587–589
729. Diengdoh JV, Scott T (1983) Electron-microscopical study of a Rathke's cleft cyst. *Acta Neuropathol (Berl)* 60:14–18
730. Diengdoh JV, Griffiths D, Crockard HA (1984) Rathke's cleft cyst. *Clin Neuropathol* 3:72–75
731. Diepholder HM, Schwachheimer K, Mohadjer M, Knoth R, Volk B (1991) A clinicopathologic and immunomorphologic study of 13 cases of ganglioglioma. *Cancer* 15:2192–2201
732. Dierssen G, Alvarez G, Figols J (1988) Anaplastic astrocytomas associated with previous radiotherapy: report of 3 cases. *Neurosurgery* 22:1095–1097
733. Diezel PB, Rottmann E (1958) Histochemische Untersuchungen an "Rosenthalschen Fasern" in Ependymgranulationen und im Spongioblastom. *Dtsch Ztschr Nervenheilkd* 177:222–234
734. Diller L, Kassel J, Nelson CE, Gryka MA, Litwak G, Gebhardt M, Bressac B, Ozturk M, Baker SJ, Vogelstein B, Friend SH (1990) p53 functions as a cell cycle control protein in osteosarcomas. *Mol Cell Biol* 10:5772–5781
735. Dinda AK, Sarkar C, Roy S (1990) Rosenthal's fibres: an immunohistochemical, ultrastructural and immunoelectron microscopic study. *Acta Neuropathol (Berl)* 79:456–460
736. Dinda AK, Kharbonda K, Sarkar C, Roy S, Mathur M, Banerji AK (1993) In vivo proliferative potential of primary brain tumors; its correlation with histological classification and morphological features: II. Nongliar tumors. *Pathology* 25:10–14
737. Dirks PB, Jay V, Becker LE, G<sup>+</sup>Drake JM, Humphreys RP, Hoffman HJ, Rutka JT (1994) Development of anaplastic changes in low-grade astrocytomas of childhood. *Neurosurgery* 34:68–78
738. Disclafani A, Hudgins RJ, Edwards MSB, Wara W, Wilson CB (1989) Pineocytomas. *Cancer* 63:302–304
739. Dobos EI, Freed GC, Ashe SMP (1953) An intrinsic tumor of the third ventricle. *J Neuropathol Exp Neurol* 12:232–243
740. Dodge HW, Love JG, McK Craig W, Dockerty MB, Kearns TP, Holman TP, Hayles CB and AB (1958) Gliomas of the optic nerves. *Arch Neur Psych* 79:607–621
741. Doglioni C, Dell'Orto P, Coggi G, Iuzzolino P, Bomtempini L, Viale G (1987) Choroid plexus tumors. An immunocytochemical study with particular reference to the coexpression of intermediate filament proteins. *Am J Pathol* 127:519–530
742. Doherty FJ, Wassell JA, Mayer RJ (1987) A putative protein sequestration site involving intermediate filaments for protein degradation by autophagy. Studies with micro-injected glycolytic enzymes. *Biochemical Journal* 241:793–800
743. Dohrmann GJ, Bucy PC (1970) Human choroid plexus: a light and electron microscopic study. *J Neurosurg* 33:506–516
744. Dohrmann GJ, Dunsmore RM (1975) Glioblastoma multiforme of the cerebellum. *Surg Neurol* 3:219–223
745. Dohrmann GJ, Farwell JR, Flannery JT (1976) Ependymomas and ependymoblastomas in children. *J Neurosurg* 45:273–283
746. Dohrmann GJ, Farwell JR, Flannery JT (1985) Astrocytomas in childhood: a population-based study. *Surg Neurol* 23:64–68
747. Dolman CL (1988) Melanotic medulloblastoma. A case report with immunohistochemical and ultrastructural examination. *Acta Neuropathol (Berl)* 76:528–531
748. Domenicucci M, Santoro A, D'Osvaldo DH, Delfini R, Cantore GP, Guidetti B (1989) Multiple intracranial meningiomas. *J Neurosurg* 70:41–44
749. Donegani G, Grattarola FR, Wildi E (1972) Tuberous sclerosis. Bourneville disease. In: Vinken PJ, Bruyn GN (eds) *Handbook of clinical neurology*, vol 14. North Holland, Amsterdam, pp 340–389
750. Donehower LA, Harvey M, Slagle BL, McArthur MJ, Montgomery CAJ, Butel JS, Bradley A (1992) Mice deficient for p53 are developmentally normal but susceptible to spontaneous tumors. *Nature* 356:215–221
751. Donnell MS, Meyer GA, Donegan WL (1979) Estrogen-receptor protein in intracranial meningiomas. *J Neurosurg* 50:499–502

752. Donoso LA, Merryman CE, Edelberg KE, Naidu R, Kalsow C (1985) S-antigen in the developing retina and pineal gland: a monoclonal antibody study. *Invest Ophthalmol Visual Sci* 26:561–567
753. Donoso LA, Felberg NT, Augsburger JJ, Shields JA (1985) Retinal S-antigen and retinoblastoma: a monoclonal antibody and flow cytometric study. *Invest Ophthalmol Visual Sci* 26:568–571
754. Donoso LA, Hann H, Dietzschold B, Augsburger JJ, Shield JA, Arbizu V (1986) Rhodopsin and histopathologic study. *Arch Ophthalmol* 109:111–113
755. Doolittle RF, Hunkapiller MW, Hood LE, Deware SG, Robbins KC, Aaronson SA, Antoniades HNL (1983) Simian sarcoma virus onc gene, v-sis, is derived from the gene (or genes) encoding a platelet-derived growth factor. *Science* 221:275–277
756. Doreen MS, Ironside JW, Bradshaw JD, Jakubowski J, Timperley WR, Hancock BW (1988) Primary intracerebral lymphoma: a clinicopathological analysis of 14 patients presenting over a 10-year period in Sheffield. *Q J Med New Series* 67:387–404
757. Dorfman RF, Burke JS, Berard CW (1982) A working formulation of non-Hodgkin's lymphomas: background, recommendations, histologic criteria and relationship to other classifications. In: Rosenberg SA, Koplan HS (eds) *Malignant lymphomas etiology, immunology, pathology, treatment*. Academic, San Francisco
758. Dorward NL, Hawkins RA, Whittle IR (1993) Epidermal growth factor receptor activity and clinical outcome in glioblastoma and meningioma. *Br J Neurosurg* 7:197–199
759. Doty JR, Schut L, Bruce DA, Sutton LN (1987) Intracranial meningiomas of childhood and adolescence. In: Kageyama N, Takakura K, Epstein F, Hoffman HJ, Schut L (eds) *Intracranial tumors in infancy and childhood*. Karger, Basel, pp 239–246
760. Doyle W, Budinger TF, Valk P (1987) Differentiation of cerebral radiation necrosis from tumor recurrence by  $^{18}\text{F}$ FDG and  $^{82}\text{Rb}$  positron emission tomography. *J Comp Ass Tomogr* 11:563–570
761. Drake JM, Hoffman HJ (1991) Meningiomas in children. In: Al-Mefty O (ed) *Meningiomas*. Raven, New York, pp 145–152
762. Draper GJ, Sanders BM, Kingston JE (1986) Second primary neoplasm in patients with retinoblastoma. *Br J Cancer* 53:661–671
763. Dritschilo A, Bruchman TE, Cassady TR, Belli JA (1981) Tolerance of brain to multiple courses of radiation therapy. I. Clinical Experiences. *Br J Radiol* 54:782–786
764. Dropcho E, Rosenfeld SS, Morawetz RB (1992) Preradiation intracarotid cisplatin treatment of newly-diagnosed anaplastic gliomas. *J Clin Oncol* 10:425–438
765. Dropcho EJ, Allen JC (1987) Primary rhabdomyosarcoma: case report and review of the literature. *J Neurooncol* 5:139–150
766. Druckrey H, Ivankovic S, Preussmann R, Zülch J, Mennel HO (1972) Selective induction of malignant tumors of the nervous system by resorptive carcinogens. In: Kirsh WM, Grossi-Paoletti E, Paoletti P (eds) *The experimental biology of brain tumors*. Thomas, Springfield, pp 85–147
767. Drut R, Jones MC (1983) Melanotic medulloblastoma of infancy. A case report with immunohistochemical study and literature review. *Morphol Norm Pathol (B)* 7:53–62
768. Dryja TP, Cavenee WK, White RL, Rapaport JM, Peterson R, Alberts DM, Bruns GAP (1984) Homozygosity of chromosome 13 in retinoblastoma. *N Engl J Med* 310:550–553
769. Du Boulay GH (1984) The plain x-ray characteristics of particular diseases of the skull and brain. In: Du Boulay GH (ed) *A textbook of radiological diagnosis*, vol 1, pp 49–53
770. Duan DR, Pause A, Burgess WH, Aso T, Chen DYT, Garrett KP, Conaway RC, Conaway JW, Linehan WM, Klausnert RD (1995) Inhibition of transcription elongation by the VHL tumor suppressor protein. *Science* 269:1402–1406
771. Dubrow R, Wegman DH (1984) Cancer and occupations in Massachusetts: a death certificate study. *Am J Ind Med* 6:207–230
772. Ducatman BS, Scheithauer BW (1983) Postirradiation neurofibrosarcoma. *Cancer* 51:1028–1033
773. Ducatman BS, Scheithauer BW (1984) Malignant peripheral nerve sheath tumors with divergent differentiation. *Cancer* 54:1049–1057
774. Ducatman BS, Scheithauer BW, Piepgras DG, Reiman HM, Ilstrup DM (1986) Malignant peripheral nerve sheath tumors. A clinicopathologic study of 120 cases. *Cancer* 57:2006–2021



775. Duckett S, Poirier J, Galle P (1978) Electron microprobe study of calcifications in human brain tumors. *Acta Neuropathol (Berl)* 44:145-146
776. Duff TA, Levine R (1983) Intrachiasmatic craniopharyngioma. Case report. *J Neurosurg* 59:176-178
777. Duffner PK, Cohen ME (1981) Extraneural metastases in childhood brain tumors. *Ann Neurol* 10:261-265
778. Duffner PK, Cohen ME, Heffner RR, Freeman AI (1981) Primitive neuroectodermal tumors of the brain cerebrum in childhood. *J Neurosurg* 55:376-381
779. Duffner PK, Cohen ME, Voorhess ML, McGillicray MH, Brecher ML, Panahon A, Gilami BB (1985) Long-term effects of cranial irradiation on endocrine function children with brain tumors: a prospective study. *Cancer* 56:2189-2193
780. Duffner PK, Cohen ME, Parker MS (1988) Prospective intellectual testing in children with brain tumors. *Ann Neurol* 23:575-579
781. Duffy PE (1983) *Astrocytes: normal, reactive and neoplastic*. Raven, New York
782. Duffy PE, Defendini R, Kremzner LT (1971) Regulation of meningioma cell growth in vitro by polyamines. *J Neuropathol Exp Neurol* 30:698-713
783. Duffy PE, Graf L, Rapport MM (1977) Identification of glial fibrillary acidic protein by the immunoperoxidase method in human brain tumors. *J Neuropathol Exp Neurol* 36:645-652
784. Duffy PE, Graf L, Huang YY, Rapport NM (1979) Glial fibrillary acidic protein in ependymomas and other brain tumors. Distribution, diagnostic criteria, and relation to formation of processes. *J Neurol Sci* 40:133-146
785. Duffy PE, Hurang YY, Graf L (1980) Glial fibrillary acidic protein in giant cell tumors of brain and other gliomas. *Acta Neuropathol (Berl)* 52:51-57
786. Duhaime AC, Bunin G, Sutton L, Rorke LB, Packer RJ (1989) Simultaneous presentation of glioblastoma multiforme in siblings two and five years old: case report. *Neurosurgery* 24:434-439
787. Duinkerke SJ, Slooff JL, Gabreëls FJM, Reiner WO, Thijssen HOM, Biesta JH (1981) Melanotic rhabdomyomedulloblastoma or teratoid tumor of the cerebellar vermis. *Clin Neurol Neurosurg* 83:29-33
788. Dukes HT, Odom GL (1962) Discrete intradural osteoma: report of a case. *J Neurosurg* 19:251-253
789. Dulic V, Kaufmann WK, Wilson SJ, Tlsty TD, Lees E, Harper JW, Elledge SJ, Reed SI (1994) p53-dependent inhibition of cyclin-dependent kinase activities in human fibroblasts during radiation-induced G1 arrest. *Cell* 76:1013-1023
790. Dumanski JP, Carlom E, Collins VP, Nordenskjöld M (1987) Deletion mapping of a locus on human chromosome 22 involved in the oncogenesis of meningioma. *Proc Natl Acad Sci USA* 84:9275-9279
791. Duncan W, McLelland J, Jack WJ (1986) Report of a randomised pilot study on the treatment of patients with supratentorial gliomas using neutron irradiation. *Br J Radiol* 59:373-377
792. Dunn J Jr (1954) Age changes in the choroid plexus of the lateral ventricle: with emphasis on calcification. Thesis, University of Minnesota
793. Duponey P, Benjelloun S, Gomes D (1985) Immunohistochemical demonstration of an organized cytoarchitecture of the radial glia in the CNS of the embryonic mouse. *Dev Neurosci* 7:81-93
794. Dutto A, Borsotti L, Cavalla P, Chiò A, Schiffer D (1995) Prognostic factors in oligodendroglioma. *Neuropathol Appl Neurobiol* 21 [Suppl 1]:42
795. Dvorak HF, Sioussat TM, Brown LF, Berse B, Nagy JA, Sotrel A, Manseau EJ, van de Water L, Senger DR (1991) Distribution of vascular permeability factor (vascular endothelial growth factor) in tumors: concentration in tumor blood vessels. *J Exp Med* 174:1275-1278
796. Dwarakanath BSR, Jain VK (1987) Modification of the radiation induced damage by 2-deoxy-d-glucose in organ cultures of human cerebral gliomas. *Int J Radiat Oncol Biol Phys* 13:741-746
797. Dyson N, Howley PM, Munager K, Harlow E (1989) The human papillomavirus-16 E7 oncoprotein is able to bind to the retinoblastoma gene product. *Science* 243:934-936
798. Earnest F, Kernohan JW, McK Craig W (1950) Oligodendrogliomas. A review of hundred cases. *Arch Neur Psych* 63:964-976

799. Easter SS, Ross LS, Frankfurter A (1993) Initial tract formation in the mouse brain. *J Neurosci* 13:285–299
800. Ebersold MJ, Morita A, Olsen KD, Quast LM (1995) Glomus jugulare tumors. In: Brain tumors, Kaye AH, Laws Jr ER (eds) Churchill Livingstone, Edinburgh, pp 795–807
801. Ectors L, Hozay J (1958) Tumeurs épidermoïdes céphaliques et rachidiennes. *Acta Neurol Psychiatr Belg* 58:655–681
802. Edwards MS, Wilson CB (1980) Treatment of radiation necrosis. In Gilbert HA, Kagan AR (eds) Radiation damage to the nervous system. Raven, New York, pp 129–143
803. Edwards MSB, Higdins RJ, Wilson CB, Levin VA, Wara WM (1988) Pineal region tumors in children. *J Neurosurg* 68:689–697
804. Ehni G, Love JG (1945) Intraspinal lipomas. Report of cases. Review of the literature, and clinical and pathological study. *Arch Neur Psych* 53:1–28
805. Ehret M, Jacobi G, Hey A, Segerer S (1987) Embryonal brain neoplasms in the neonatal period and early infancy. *Clin Neuropathol* 6:218–223
806. Eisenbarth GS, Walsh FS, Nirenberg M (1979) Monoclonal antibody to a plasma membrane antigen in neurons. *Proc Natl Acad Sci USA* 76:4913–4917
807. Eiser C (1979) Intellectual development following treatment for childhood leukaemia. In: Whitehouse JMA, Kay HEM (eds) CNS complications of malignant disease. Macmillan, London, pp 236–250
808. Ekstrand AJ, James CD, Cavenee WK, Seliger D, Petterson RF, Collins VP (1991) Genes for epidermal growth factor receptor and transforming growth factor  $\alpha$ , epidermal growth factor and their expression in human gliomas in vivo. *Cancer Res* 51:2164–2172
809. Ekstrand AJ, Sugawa N, James CD, Collins VP (1992) Amplified and rearranged epidermal growth factor receptor genes in human glioblastomas reveal deletions of sequences encoding portions of the N-and/or C-terminal tails. *Proc Natl Acad Sci USA* 89:4309–4313
810. El-Azouzi, Chung QY, Farmer GE, Martuza RL, Black PMcL, Rouleau GA, Hettlich C, Hedley-White ET, Zervas NT, Panagopoulos K, Nakamura Y, Gusella SF, Seizinger BR (1989) Loss of distinct regions on the short arm of chromosome 17 associated with tumorigenesis of human astrocytomas. *Proc Natl Acad Sci USA* 86:7186–7190
811. el-Deiry WS, Tokino T, Velculescu VE, Levy DB, Parsons , Trent JM, Lin D, Mercer WE, Kinzler KW, Vogelstein B (1993) WAF1, a potential mediator of p53 tumor suppression. *Cell* 75:817–825
812. El-Hennawi Y, Gillespie GY, Mahaley MS Jr, Baria VA, Bigner DD, Stanton C (1989) A controlled study of efficacy of interstitial or external irradiation in a virus induced brain-tumor model in rats. *J Neurosurg* 71:898–902
813. Elam EB, McLaurin RL (1961) Multiple primary intracranial tumors. Case report. *J Neurosurg* 18:388–392
814. Eldridge AR, Penfield W, Cone W (1935) The gliomas of the central nervous system. *Proc Ass Res Nerv Ment Dis* 16:107–115
815. Eljamel MSM, Foy PM (1989) Multiple meningiomas and their relation to neurofibromatosis. Review of the literature and report of seven cases. *Surg Neurol* 31:131–136
816. Ellams ID, Neuhäusen G, Agnoli AL (1986) Congenital intracranial neoplasm. *Childs Nerv Syst* 2:165–168
817. Ellenbogen RG, Winston KR, Kupsky WJ (1989) Tumors of the choroid plexus in children. *Neurosurgery* 25:327–335
818. Ellis PSJ, Whitehead R (1981) Mitosis counting: a need for reappraisal. *Hum Pathol* 12:3–4
819. Ellison DW, Steart PV, Bateman AC, Pickering RM, Palmer JD, Weller RO (1995) Prognostic indicators in a range of astrocytic tumours: an immunohistochemical study with Ki-67 and p53 antibodies. *J Neurol Neurosurg Psych* 59:413–419
820. Ellison DW, Steart PV, Gatter KC, Weller RO (1995) Apoptosis in cerebral astrocytic tumours and its relationship to expression of the bcl-2 and p53 proteins. *Neuropathol Appl Neurobiol* 21:352–361
821. Ellmeier W, Aguzzi A, Kleiner E, Kurzbauer R, Weith A (1992) Mutually exclusive expression of a helix-loop-helix gene and N-myc in human neuroblastomas and in normal development. *EMBO J* 11:2563–2571
822. Elvidge AR (1968) Long term survival in the astrocytoma series. *J Neurosurg* 28:399–404

823. Elvidge AR, Penfield W, Cone W (1935) The gliomas of the central nervous system. *Proc Ass Res Nerv Ment Dis* 16:107–137
824. Eng C, Li FP, Abramson DH, Ellsworth RM, Wong FL, Goldman MB, Seddon J, Tarbell N, Boice JD (1993) Mortality from second tumors among long-term survivors of retinoblastoma. *J Natl Cancer Inst* 85:1121–1128
825. Eng LF, Bigbee JW (1978) Immunohistochemistry of the nervous system antigens. In: Agranoff BW, Aprison MH (eds) *Advances in neurochemistry*, vol 3. Plenum, New York, pp 43–98
826. Eng LF, De Armond SJ (1983) Immunocytochemistry of the glial fibrillary acidic protein. In: Zimmerman HM (ed) *Progress in neuropathology*, vol 5. Raven, New York, pp 19–39
827. Eng LF, Lee YL (1994) Intermediate filaments in astrocytes. In: Ransom BR, Kethemba H (eds) *Neuroglial cells*. Oxford University Press, New York
828. Eng LF, Rubinstein LF (1978) Contribution of immunohistochemistry to diagnostic problems of human cerebral tumors. *J Histochem Cytochem* 26:513–522
829. Eng LF, Vanderhaeghen JJ, Bignami A, Gerstl B (1971) An acidic protein isolated from fibrous astrocytes. *Brain Res* 28:351–354
830. Engelhard HH, Butler AB, Bauer KD (1989) Quantification of the c-myc oncoprotein in human glioblastoma cells and tumor tissue. *J Neurosurg* 71:224–232
831. Engelhardt A, Bannasch P (1978) Histochemie säuer Mucopolysaccharide während der Genese Methylnitrososoharnstoffinduzierter Hirntumoren der Ratte. *Acta Neuropathol (Berl)* 42:197–204
832. Englund A, Ekman G, Zabrielski L (1981) Occupational categories among brain tumor cases recorded in the cancer registry in Sweden. *Ann NY Acad Sci* 381:188–196
833. Engström A, Fincan JB (1953) Biological ultrastructure. Academic, New York
834. Enomoto H, Shibata T, Ito A, Harada T, Satake T (1984) Multiple hemangioblastomas accompanied by syringomyelia in the cerebellum and the spinal cord. *Surg Neurol* 22:197–203
835. Enzinger FM, Weiss SW (1983) *Soft tissue tumors*. Mosby, St Louis
836. Enzinger FM, Weiss SW (1988) *Soft tissue tumors*. Mosby, St Louis
837. Epstein F (1987) Intrinsic brain stem tumors of childhood. Surgical indications. In: Kageyama N, Takakura, Epstein F, Hoffman HJ, Schut L (eds) *Intracranial tumors in infancy and childhood*. *Prog Exp Tumor Res* 30:160–169
838. Erbslöh F, Bochnik HJ (1958) Symmetrische Pseudokalk- und Kalkablagerungen im Gehirn. Sogenannte "idiopathische" nicht arteriosklerotische intracerebrale Gefäßverkalkungen (Fahr). In: Lubarsch O, Henke F, Rössle R (eds) *Handbuch der speziellen pathologischen Anatomie und Histologie*, vol 13. Springer, Berlin Göttingen Heidelberg
839. Erdheim J (1904) Über Hypophysenganggeschwülste und Hirncholesteatome: Sitzungsberichte der Akademie der Wissenschaft, Vienna. *Math-Natl Kl* 113:537–726
840. Erisman MD, Astrin SM (1988) The myc oncogene. In: Reddy EP, Skalka AM, Curran T (eds) *The oncogene handbook*. Elsevier, Amsterdam, pp 341–379
841. Erlandson RA (1984) Diagnostic immunohistochemistry of human tumors. An interim evaluation. *Am J Surg Pathol* 8:615–624
842. Erlandson RA (1985) Peripheral nerve sheath tumors. *Ultrastr Pathol* 9:113–122
843. Erlandson RA, Tandler B, Lieberman PH, Higinbotham NL (1968) Ultrastructure of human chordoma. *Cancer Res* 28:2115–2125
844. Erlich SS, Apuzzo LJ (1985) The pineal gland: anatomy, and clinical significance. *J Neurosurg* 63:321–341
845. Ermel AE, Brucher JM (1974) Arguments ultrastructuraux en faveur de l'appartenance du médulloblastome à la lignée neuronale. *Acta Neurol Belg* 74:208–220
846. Ervin T, Canellos GP (1980) Successful treatment of recurrent primary central nervous system lymphoma with high-dose methotrexate. *Cancer* 45:1556–1556
847. Escalona-Zapata J, Diez Nau MD (1978) The nature of macrophages (foam cells) in neurinomas. Tissue culture study. *Acta Neuropathol (Berl)* 44:71–75
848. Escalona-Zapata J, Salinero E, Lacruz C (1981) Malignant cerebellar gliomas. Report of 4 cases with special reference to tissue culture study. *J Neurosurg Sci* 25:95–104
849. Escourolle R, Poirier J (1971) Étude en microscopie électronique des tumeurs du système nerveux. In: Le Beau J (ed) *Méthodes morphologiques modernes en neuro-chirurgie*, Neurochir (Paris) pp 1:25–49

850. Esiri MM, McGee JOD (1986) Monoclonal antibody to macrophages (EBM11) labels macrophages and microglial cells in human brain. *J Clin Pathol* 39:615–621
851. Espana P, Chang P, Wiernik PG (1980) Increased incidence of brain metastases in sarcoma patients. *Cancer* 45:377–380
852. Essbach H (1943) Die Meningeome vom Standpunkt der organoiden Geschwulstbetrachtung. *Ergeb Allg Pathol* 36:185–490
853. Evan GI, Wyllie AH, Gilbert CS, Littlewood TD, Land H, Brooks M, Waters CM, Penn LZ, Hancock DC (1992) Induction of apoptosis in fibroblasts by c-myc protein. *Cell* 69:119–128
854. Evans AE, Jenkin DT, Sposto R, Ortega JA, Wilson CB, Wara W, Ertel IJ, Kramer S, Chang CH, Leikin SL, Hammond GD (1990) The treatment of medulloblastoma. Results of a prospective randomized trial of radiation therapy with and without CCNU, vincristine, and prednisone. *J Neurosurg* 75:572–582
855. Evans RV (1957) Developmental stages of embryo-like bodies in teratoma testis. *J Clin Pathol* 10:31–39
856. Fabiani A (1964) Considerazioni sul processo di ossificazione nei meningiomi, con presentazione di 3 casi. *Riv Pat Nerv Ment* 85:95–104
857. Fabiani A, Monticone GF (1964) Considerazioni su di un raro caso di meningioma calcificato. *Riv Neurobiol* 10:390–397
858. Fabiani A, Lombard GF, Monticone GF (1964) Considerazioni sul problema delle metastasi extracraniche dei tumori gliali con presentazione di un caso. *Cancro* 17:196–205
859. Fabiani A, Trebini F, Favero M, Peres B, Palmucci L (1977) The significance of atypical mitoses in malignant meningiomas. *Acta Neuropathol (Berl)* 38:229–231
860. Fadul C, Fracp JW, Thaler H, Galicich J, Patterson RH, Posner JB (1988) Morbidity and mortality of craniotomy for excision of supratentorial gliomas. *Neurology* 38:1374–1379
861. Fain JS, Tomlinson FH, Scheithauer BW, Parisi JE, Fletcher GF, Kelly PJ, Miller GM (1994) Symptomatic glial cysts of the pineal gland. *J Neurosurg* 80:454–460
862. Faiss J, Wild G, Schroth G, Heiss E, Melms A (1991) Multiple supratentorial hemangioblastomas following primary infratentorial manifestation. *Clin Neuropathol* 10:21–25
863. Falk W, Goodwin RH, Leonard EJ (1980) A 48-well micro chemotaxis assembly for rapid and accurate measurement of leukocyte migration. *J Immunol Methods* 33:239–247
864. Fan KJ, Kovi J, Earle KM (1977) The ethnic distribution of primary central nervous system tumours: Armed Forces Institute of Pathology, 1958–1970. *J Neuropathol Exp Neurol* 36:41–49
865. Farrell CL, Stewart PA, Del Maestro RF (1987) A new glioma model in rat: the C6 spheroid implantation technique permeability and vascular characterization. *J Neurooncol* 4:403–415
866. Farmer J-P, Antel JP, Freedman M, Cashman NR, Rode H, Villemure JG (1989) Characterization of lymphoid cells isolated from human gliomas. *J Neurosurg* 71:528–533
867. Farwell J, Flannery JT (1984) Cancer in relatives of children with central-nervous system neoplasm. *N Engl J Med* 311:749–753
868. Farwell J, Dohrmann G, Flannery JT (1984) Medulloblastoma in childhood: an epidemiological study. *J Neurosurg* 61:657–664
869. Federico F, D'Aprile P, Lorusso A, Belsanti M, Carella A (1984) Multiple meningiomas diagnosed by computed tomography. *Ital J Neurol Sci* 5:295–298
870. Fedoroff S, White R, Neal J, Subrahmanian L, Kalnins VI (1983) Astrocyte cell lineage. II Mouse fibrous astrocytes and reactive astrocytes in cultures have vimentin and GFAP containing intermediate filaments. *Dev Brain Res* 7:303–315
871. Fedoroff S, McAuley WJ, Houle JD, Devon RM (1984) Astrocyte cell lineage. V. Similarity of astrocytes that form in the presence of dBcAMP in cultures to reactive astrocytes in vivo. *J Neurosci Res* 12:15–27
872. Feiden W, Bise K, Mehraein P (1988) Differential diagnosis of malignant CNS lymphomas on surgical and stereotactic brain biopsies by means of immunohistochemistry with monoclonal antileukocyte antibodies (DAKO-L26, -UCHL1, -MAC387, -LC, MBI, MB2). *Clin Neuropathol* 7:162
873. Feigin I, Gross SW (1955) Sarcoma arising in glioblastoma of brain. *Am J Pathol* 31:633–653
874. Feigin I, Ogata J (1971) Schwann cells and peripheral myelin within human central nervous tissue: the mesenchymal character of Schwann cells. *J Neuropathol Exp Neurol* 30:603–612
875. Feigin I, Allen LB, Lipkin L, Gross SW (1958) The endothelial hyperplasia of the cerebral blood vessels with brain tumors and its sarcomatous transformation. *Cancer* 11:264–277

876. Feigin I, Budzilovich G, Weinberg S, Ogata U (1973) Degeneration of white matter in hypoxia, acidosis and edema. *J Neuropathol Exp Neurol* 32:125–143
877. Feigin I, Ransohoff J, Lieberman A (1976) Sarcoma arising in oligodendrogliomas of the brain. *J Neuropathol Exp Neurol* 35:679–684
878. Feigin I, Epstein F, Mangiardi J (1983) Extensive advanced maturation of medulloblastoma to astrocytoma and ependymoma. *J Neurooncol* 1:95–108
879. Feindel W, Diksic M, Yamamoto L, Arnold D, Shoubbridge E, Willemure JG (1989) Access of drugs into gliomas. In: Broggi G, Gerosa MA (eds) *Cerebral gliomas*. Excerpta Medica, Amsterdam, pp 241–250
880. Feiring EH, Barron K (1962) Late recurrence of spinal-cord meningioma. *J Neurosurg* 19:652–656
881. Fekete I, Griffith OW, Schlageter KE, Bigner DD, Friedman HS, Groothuis DR (1990) Rate of buthionine sulfoximine entry into brain and xenotransplanted human gliomas. *Cancer Res* 50:1251–1256
882. Felix I, Bilbao JM, Asa SL, Tyndel F, Kovacs K, Becker LE (1994) Cerebral and cerebellar gangliocytomas: a morphological study of nine cases. *Acta Neuropathol (Berl)* 88:246–253
883. Fenselau A, Watt S, Mello RJ (1981) Tumor angiogenetic factor. *J Biol Chem* 256:9605–9611
884. Fényes G, Kepes J (1956) Über das gemeinsame Vorkommen von Meningeomen und Geschwülsten anderen Typs im Gehirn. *Zbl Neurochir* 16:251–260
885. Fernandes-Alnemri T, Litwack G, Alnemri ES (1994) CPP32, a novel human apoptotic protein with homology to *Caenorhabditis elegans* cell death protein Ced-3 and mammalian interleukin-1 $\beta$ -converting enzyme. *J Biol Chem* 269:30761–30764
886. Fernandez LA, Twickler J, Mead A (1985) Neovascularization produced by angiotensin II. *J Lab Clin Med* 105:141–145
887. Ferrante L, Celli P, Fraioli B (1982) Supratentorial hemangioblastomas in children: case report. *Acta Neurochir (Wien)* 62:241–246
888. Ferrante L, Acqui M, Artico M, Mastronardi L, Rocchi G, Fortuna A. (1989) Cerebral meningiomas in children. *Childs Nerv Syst* 5:83–86
889. Ferrara N, Henzel WJ (1989) Pituitary follicular cells secrete a novel heparin-binding growth factor specific for vascular endothelial cells. *Biochem Biophys Res Commun* 161:851–858
890. Ferrer I, Ysamat F, Acebe J (1979) A Golgi and electron microscopic study of a dysplastic gangliocytoma of the cerebellum. *Acta Neuropathol (Berl)* 47:163–165
891. Fertil B, Malaise EP (1985) Intrinsic radiosensitivity of human cell lines is correlated with radioresponsiveness of human tumors: analysis of 101 published survival curves. *Int J Radiat Oncol Biol Phys* 11:1699–1707
892. Fett JW, Strydom DS, Lobb RR, Bethune JL, Alderman EM, Riordan JF, Vallee BL (1985) Isolation and characterization of angiogenin, an angiogenic protein from human carcinoma cells. *Biochemistry* 24:5480–5486
893. Fidler IJ (1984) The evolution of biological neoplasms. In: Nicolson JL, Milas L (eds) *Cancer invasions and metastasis: biologic and therapeutic aspects*. Raven, New York, pp 5–20
894. Figarella-Branger D, Gambarelli D, Dollo C, Devictor B, Perez-Castillo AM, Genitori L, Lena G, Choux M, Pellissier JF (1991) Infratentorial ependymomas of childhood. Correlation between histological features, immunohistological phenotype, silver nucleolar organizer region staining values and post-operative survival in 16 cases. *Acta Neuropathol (Berl)* 82:208–216
895. Figarella-Branger D, Vagner-Capodano AM, Bouillott P, Grazianit N, Gambarelli D, Devictor B, Zattara-Cannoni H, Bianco N, Grisoli F, Pellissier JF (1994) Platelet-derived growth factor (PDGF) and receptor (PDGFR) expression in human meningiomas: correlations with clinicopathological features and cytogenetic analysis. *J Neuropathol Appl Neurobiol* 20:439–447
896. Fike JR, Sheline GE, Cann CE, Davis RL (1984) Radiation necrosis. *Prog Exp Tumor Res* 28:136–151
897. Fincher EF, Coon GP (1929) Ependymomas. *Arch Neurol Psych* 22:19–24
898. Findlay JM, Akabutu J, Johnson ES, McDonald S (1994) Radiation-induced meningioma. *J Neurosurg* 80:594
899. Fine HA (1995) Novel biologic therapies for malignant gliomas. Antiangiogenesis, immunotherapy and gene therapy. In: Wen PI, Black PM (eds) *Brain tumors in adults*. Saunders, Philadelphia, pp 827–846 (*Neurologic clinic* 13/4)

900. Fingert HJ, Hochberg FH (1984) Megadose chemotherapy with bone marrow rescue. In: Rosenblum ML, Wilson CB (eds) Progress in experimental tumor research. Brain tumor therapy, vol 28. Karger, Basel, pp 67–78
901. Fink KL, Rushing EJ, Schold Jr SC, Nisen PD (1996) Infrequency of p53 gene mutations in ependymomas. *J Neurooncol* 27:111–115
902. Finkenmeyer H, Behrend RC (1956) Hirntrauma und Gliomentstehung. *Zbl Neurochir* 16:318–324
903. Finlay JL (1986) Natural history and epidemiology of medulloblastoma. In: Zelter PM, Pochedly C (eds) Medulloblastoma in children. New concepts in tumor biology, diagnosis and treatment. Praeger, New York, p 22–31
904. Firsching RP, Doz P, Fischer A, Peters R, Thun F, Klug N (1990) Growth rate of incidental meningiomas. *J Neurosurg* 73:545–547
905. Fischer EG, Welch K, Belli JA, Shillito JJ, Winston KR, Cassady R (1985) Treatment of cranio-pharyngiomas in children: 1972–1981. *J Neurosurg* 62:496–501
906. Fischer EG, Welch K, Shillito J Jr, Wiston KR, Tarbell NJ (1990) Craniopharyngiomas in children. *J Neurosurg* 73:534–540
907. Fischer G, Mansuy L (1980) Total removal of intramendullary ependymomas: follow-up study of 16 cases. *Surg Neurol* 14:243–249
908. Fisher ER, Wechsler H (1962) Granular cell myoblastoma—a misnomer. EM and histochemical evidence concerning its Schwann cell derivation and nature (granular cell schwannoma). *Cancer* 15:936–942
909. Fisher RG (1968) Intracranial meningioma followed by malignant glioma. Case report. *J Neurosurg* 29:83–86
910. Fishman RA (1975) Brain edema. *N Engl J Med* 293:706–711
911. Fishman RA (1980) Cerebrospinal fluid in diseases of the nervous system. Sanders, Philadelphia, pp 128–139
912. Fishman RA (1987) Is there a therapeutic role for osmotic breaching of the blood brain barrier? *Ann Neurol* 22:298–299
913. Fishman RA, Chan PM (1981) Hypothesis: membrane phospholipid degradation and polyunsaturated fatty acids play a key role in the pathogenesis of brain edema. *Trans Am Neurol Assoc* 106:58–61
914. Fitzgibbons PL, Turner RR, Apply AJ, Bishop PC, Nichols PW, Epstein AL, Apuzzo MLJ, Chandrasoma PT (1988) Flow cytometric DNA and nuclear antigen content in astrocytic neoplasms. *Am J Clin Pathol* 88:640–644
915. Fletcher CDM, Davies SE, McKee PH (1987) Cellular Schwannoma: a distinct pseudosarcomatous entity. *Histopathology* 11:21–35
916. Flickenger JC, Torres C, Deutsch M (1988) Management of low-grade gliomas of the optic nerve and chiasm. *Cancer* 61:635–642
917. Flickinger J, Nelson P, Taylor F, Robinson A (1989) Incidence of cerebral infarction after radiotherapy for pituitary adenoma. *Cancer* 63:2404–2408
918. Flowers A, Levin VA (1995) Chemotherapy for brain tumors. In: Brain tumors. Kaye AH, Laws ER Jr (eds) Churchill Livingstone, New York, pp. 349–360
919. Foerster O, Gagel O (1934) Zentrale diffuse Schwannose bei Recklinghausenscher Krankheit. *Z Gesamte Neurol Psychiatr* 151:1–16
920. Foerster O, Gagel O (1939) Das umschriebene Arachnoidsarkom des Kleinhirns. *Z Gesamte Neurol Psychiatr* 164:565–586
921. Fogelholm R, Untela T, Munos K (1984) Epidemiology of central nervous system neoplasms. A regional survey in central Finland. *Acta Neurol Scand* 69:129–136
922. Fokes EC, Earle KM (1969) Ependymomas: clinical and pathological aspects. *J Neurosurg* 30:585–594
923. Folkman J (1982) Angiogenesis: initiation and control. *Ann NY Acad Sci* 401:212–227
924. Folkman S, Klagsbrun M (1987) Angiogenic factors. *Science* 235:442–447
925. Fontaine B, Hanson MP, Von Sattel JP, Martuze RL, Gusella JF (1991) Loss of chromosome 22 alleles in human sporadic spinal schwannomas. *Ann Neurol* 29:183–186
926. Fontana A, Hengertner H, de Tribolet N, Weber E (1984) Glioblastoma cells release both interleukin 1 and factors inhibiting interleukin 2 mediated effects. *J Immunol* 132:1837–1844

927. Fontana M, Stanton C, Pompili A, Amadori S, Mandelli F, Meloni G, Riccio A, Rubinstein LJ (1987) Late multifocal gliomas in adolescents previously treated for acute lymphoblastic leukemia. *Cancer* 60:1510–1518
928. Fontana A, Bodmer S, Frei K, Malipiero U, Siepl C (1991) Expression of TGF-beta2 in human glioblastoma: a role in resistance to immune rejection? *Ciba Found Symp* 157:232–241
929. Foo SH, Choi IS, Barenstein A, Wise A, Ransohoff J, Koslow M, George A, Lin J, Feigin I, Budzilovich G, Kupersmith M, Hanson R, Lequeric A, Aleksic S, Kricheff I (1986) Supraophthalmic intracarotid infusion of BCNU for malignant glioma. *Neurology* 36:1437–1444
930. Fornatto L, Schiffer D (1972) In vitro culture observations on neurinoma induced experimentally in the rat by ethylnitrosourea. *Acta Neuropathol (Berl)* 20:199–206
931. Fornatto L, Portaleone P, Schiffer D (1972) Sulla comparsa familiare dell'angioblastoma cerebellare solitario e sui suoi rapporti con il complesso Von Hippel–Lindau. *Acta Neurol (Napoli)* 27:286–290
932. Forsyth PA, Cairncross JG (1995) Treatment of malignant gliomas in adults. *Curr Opin Neurol* 8:414–418
933. Forsyth PA, Cascino TL, Shaw EG, Scheithauer BW, O'Fallon JR, Dozier JC, Piepgres DG (1993) Intracranial chordomas: a clinicopathological and prognostic study of 51 cases. *J Neurosurg* 78:741–747
934. Forsyth PA, Kelly PJ, Cascino TL, Scheithauer BW, Shaw EG, Dinapoli RP, Atkinson EJ (1995) Radiation necrosis or glioma recurrence: is computer-assisted stereotactic biopsy useful? *J Neurosurg* 82:436–444
935. Forti E, Venturini G (1960) Contributo alla conoscenza delle neoplasie notocordali. *Riv Anat Pat Oncol* 17:317–396
936. Fotakis NS (1961) Über die formale Genese von Keratinformationen in Kraniopharyngiomen (Erdheim-Tumor). *Dtsch Ztschr Nervenheilkd* 181:581–592
937. Foulds L (1958) The natural history of cancer. *J Chronic Dis* 8:2–11
938. Fowler M, Simpson DA (1962) A malignant melanin-forming tumour of the cerebellum. *J Pathol Bacteriol* 84:307–311
939. Fox JL (1991) Meningiomas and associated lesions. In: Al-Mefty O (ed) *Meningiomas*. Raven, New York, pp 129–136
940. Francavilla TL, Miletich RS, DiChiro G, Patronas NJ, Rizzoli HV, Wright DC (1989) Positron emission tomography in the detection of malignant degeneration of low-grade gliomas. *Neurosurgery* 24:1–5
941. France LH (1968) Contribution à l'étude des métastases cérébrales. I. Corrélations anatomocliniques de 150 cas. *Min Neurochir* 12:195–209
942. François J, Ectors L, Verriest G (1958) Le cholestéatome de l'orbite. *Acta Neur Psychiatr Belg* 58:699–712
943. Frank G, Ferracini R, Spagnolli F, Frank F, Gainst G, Lorenzini P, Ricci R (1985) Primary intracranial lymphomas. *Surg Neurol* 23:3–8
944. Franke FE, Altmannsberger M, Schachenmayr W (1990) Metastasis of renal carcinoma colloidizing with glioblastoma. *Acta Neuropathol (Berl)* 80:448–452
945. Franke WW, Schmidt E, Winter S, Osborn M, Weber K (1979) Widespread occurrence of intermediate-sized filaments of the vimentin-type in cultured cells from diverse vertebrates. *Exp Cell Res* 123:25–46
946. Franke FE, Schachenmayr W, Osborn M, Altmannsberger M (1991) Unexpected immunoreactivities of intermediate filament antibodies in human brain and brain tumors. *Am J Pathol* 139:67–79
947. Frankel RH, Bayona W, Koslow M, Newcomb EW (1992) p53 mutations in human malignant gliomas: comparison of loss of heterozygosity with mutation frequency. *Cancer Res* 52:1427–1433
948. Franko MC, Masters CL, Gibbs CJ Jr, Gajdusek DC (1981) Monoclonal antibodies to central nervous system antigens. *J Neuroimmunol* 1:391–411
949. Fraser H (1986) Brain tumours in mice, with particular reference to astrocytoma. *Food Chem Toxicol* 24:105–111
950. Frattola L, Canal N, Ferrarese C, Gaini SM, Tonini C, Trabucchi M (1981) Characteristics of the cyclic AMP-phosphodiesterase activator in human brain tumours. *J Neurol Sci* 52:269–277

951. Frattola L, Canal N, Ferrarese C, Tonini C, Tonon G, Villani R, Trabucchi M (1983) Multiple forms of protein kinase from normal human brain and glioblastoma. *Cancer Res* 43:1321–1324
952. Frazier CH, Alpers BJ (1931) Adamantinoma of the craniopharyngeal duct. *Arch Neurol Psychiatry* 26:905–965
953. Frederiksen K, McKay RDG (1988) Proliferation and differentiation of rat neuroepithelial precursor cells in vivo. *J Neurosci* 8:1144–1151
954. Frederiksen P, Reske-Nielsen E, Bichel P (1978) Flow cytometry in tumours of the brain. *Acta Neuropathol (Berl)* 41:179
955. Freedman H, Forster FM (1948) Bone formation and destruction in meningiomas. *J Neuropathol Exp Neurol* 7:69–80
956. Freeman AI, Fenstermacher J, Shapiro W, Kemshead J, Chasin M, Colvin OM, Diksic M, Finley J, Hertler A, Levin V, Mayhew E, Poplack D, Shapiro J, Ushio Y (1990) Forbeck forum on improved drug delivery to brain tumors. *Selective Cancer Therapeut* 6:109–118
957. Freeman C, Berg JW, Centler SJ (1972) Occurrence and prognosis of extranodal lymphomas. *Cancer* 29:252–260
958. Freeman CR, Shustik C, Brisson ML, Meagher-Villemure K, Dylewski I (1986) Primary malignant lymphoma of the central nervous system. *Cancer* 58:1106–1111
959. Freeman L, Feigin D (1963) Oligodendroglioma with 35 years of survival. *J Neurosurg* 20:363–365
960. Frei K, Bodmer S, Schwerdel C, Fontana A (1985) Astrocytes of the brain synthesize interleukin-3-like factors. *J Immunol* 135:4044–4047
961. Freilich RJ, De Angelis LM (1995) Primary central nervous system lymphoma. *Neurol Clin* 13:901–914
962. French JP, Bucy PC (1948) Tumors of septum pellucidum. *J Neurosurg* 5:433–449
963. Freshney RI (1980) Tissue culture of glioma of the brain. In: Thomas DGT, Graham DI (eds) *Brain tumors*, Butterworths, London, pp 21–50
964. Friede RL (1962) Cytochemistry of normal and reactive astrocytes. *J Neuropathol Exp Neurol* 21:471–478
965. Friede RL (1978) Gliofibroma. A peculiar neoplasia of collagen forming glia-like cells. *J Neuropathol Exp Neurol* 37:300–313
966. Friede RL, Pollack A (1978) The cytogenetic basis for classifying ependymomas. *J Neuropathol Exp Neurol* 37:103–118
967. Friedman HS, Burger PC, Bigner SH, Trojanowski JQ, Wikstrand CJ, Halperin EC, Bigner DD (1985) Establishment and characterization of the human medulloblastoma cell line and transplantable xenograft D283 Med. *J Neuropathol Exp Neurol* 44:592–605
968. Friedman HS, Burger PC, Bigner SH, Trojanowski JQ, Brodeur GM, He X, Wikstrand CJ, Kurtzberg J, Berens ME, Halperin EC, Bigner DD (1988) Phenotypic and genotypic analysis of a human medulloblastoma cell line and transplantable xenograft (D341 Med) demonstrating amplification of c-myc. *Am J Pathol* 130:472–484
969. Friedman HS, Griffith OW, Colvin OM, Elion CB, Bigner SH, Halperin EC, Lippitz B, Schold SC, Ostertag CB, Bigner DD (1989) Therapeutic consequences of glutathione depletion. *J Neurooncol [Suppl]* 7:37
970. Friedmann I, Harrison OFN, Bird ES (1962) Fine structure of chordoma with particular reference to physaliferous cell. *J Clin Pathol* 14:116–125
971. Friend SH, Bernhards R, Rpgelj S, Winberg RA, Rapaport JM, Albert DM, Dryja TP (1986) A human DNA segment with properties of the gene predisposes to retinoblastoma and osteosarcoma. *Nature* 323:643–646
972. Friend SH, Horowitz JM, Gerber MR, Wang XF, Bogenmann E, Li FP, Weinberg RA (1987) Deletions of a DNA sequence in retinoblastomas and mesenchymal tumours: organization of the sequence and its encoded protein. *Proc Natl Acad Sci USA* 84:9059–9063
973. Frizzera G, Rosai J, Dehner LP, Spector BD, Kersey JM (1980) Lymphoreticular disorders in primary immunodeficiencies: new findings based on an up-to-date histologic classification of 35 cases. *Cancer* 46:692–699
974. Froman C, Lipschitz R (1970) Demography of tumors of the central nervous system among the Bantu (African) population of the Transvaal, South Africa. *J Neurosurg* 32:660–664



975. Frost PJ, Laperriere NJ, Wong CS, Milosevic ME, Simpson WJS, Pintilie M (1995) Medulloblastoma in adults. *Int J Radiation Oncology Biol Phys* 4:951–957
976. Fryer AE, Chalmers A, Connor JM, Fraser I, Poverly S, Yates AD, Yates JRW, Osborne JP (1987) Evidence that the gene for tuberous sclerosis is on chromosome 9. *Lancet* 1:659–661
977. Frytak S, Earnest IV F, O'Neill BP, Lee RE, Creagan ET, Trautmann JC (1985) Magnetic resonance imaging for neurotoxicity in long-term survivors of carcinoma. *Mayo Clin Proc* 60:803–812
978. Fu YS, Chen ATL, Kay S, Young HF (1974) Is subependymoma (subependymal glomerate astrocytoma) an astrocytoma or ependymoma? A comparative ultrastructural and tissue culture study. *Cancer* 34:1992–2008
979. Fu YS, Gabbiani G, Kaye GI, Lattes R (1975) Malignant soft tissue tumors of probable histiocytic origin (malignant fibrous histiocytomas): general considerations and electron microscopic and tissue culture studies. *Cancer* 35:176–198
980. Fujii M, Nishikawa A, Tanaka T, Mori H, Takahashi M, Sakai N, Yamada H (1984) Cytochemical changes in lactate dehydrogenase isoenzymes in human brain tumours. *Acta Neurochir (Wien)* 71:243–253
981. Fujimaki T, Matsutani M, Nakamura O, Asai A, Funada N, Koike M, Segawa H, Aritake K, Fukushima T, Honjo, Tamura A, Sano K (1991) Correlation between bromodeoxyuridine-labeling indices and patient prognosis in cerebral astrocytic tumors of adults. *Cancer* 67:1629–1634
982. Fujimoto M, Yoshino E, Hirakawa K, Fujimoto J, Tamaya T (1984) Estrogen receptors in brain tumors. *Clin Neuropharm* 7:357–362
983. Fujimoto M, Fufts DW, Thomas GA, Nakamura Y, Heilbrun MT, White R, Story JL, Naylor SL, Kagan-Hallet S, Sheridan PJ (1989) Loss of heterozygosity on chromosome 10 in human glioblastoma multiforme. *Genomics* 4:210–214
984. Fujimoto M, Sheridan PJ, Sharp D, Weaker FJ, Kagan-Hallet KS, Story JL (1989) Proto-oncogene analyses in brain tumors. *J Neurosurg* 70:910–915
985. Fujita H, Fujita S (1963) Electron microscopic studies on neuroblast differentiation in the central nervous system of domestic fowl. *Z Zellforsch Mikrosk Anat* 60:463–478
986. Fujita S (1963) The matrix cell and citogenesis in the developing central nervous system. *J Comp Neurol* 120:37–42
987. Fujita S (1965) The matrix cell and citogenesis of the nervous system. *Laval Med* 36:125–130
988. Fujita S (1966) Application of light and electron microscopic autoradiography to the study of cytogenesis of the forebrain. In: Hassler R, Stephan H (eds) *Evolution of the forebrain*. Plenum, New York, pp 180–196
989. Fujiwara S, Takaki T, Hikita T, Nishio S (1989) Subependymal giant-cell astrocytoma associated with tuberous sclerosis. Do subependymal nodules grow? *Childs Nerv Syst* 5:43–44
990. Fukui M, Tanaka A, Kitamura K, Okudera K (1977) Lipoma in the cerebellopontine angle: case report. *J Neurosurg* 46:544–547
991. Fukui M, Kitamura K, Nakagaki H, Yamakawa Y, Kinoshita K, Hayabuchi N, Jingu K, Numaguchi Y, Matsura K, Watanabe K (1980) Irradiated meningiomas: a clinical evaluation. *Acta Neurochir (Wien)* 54:33–43
992. Fukui M, Iwaki T, Sawa H, Inoue T, Takeshita I, Kitamura K (1986) Proliferative activity of meningiomas as evaluated by bromodeoxyuridine uptake examination. *Acta Neurochir (Wien)* 81:135–141
993. Fukuma S, Takemoto S, Ueda S et al (1969) Autoradiographic studies on human brain tumors using local labeling with [3H]-thymidine in vivo (Japanese). *Brain Nerve (Tokyo)* 21:1029–1035
994. Fuller GN, Bigner SH (1992) Amplified cellular oncogenes in neoplasms of the human central nervous system. *Mut Res* 276:299–306
995. Fulling KH, Garcia DM (1985) Anaplastic astrocytoma of the adult cerebrum: Prognostic value of histologic features. *Cancer* 55:928–931
996. Fufts D, Tippetts RH, Thomas GA, Nakamura Y, White R (1989) Loss of heterozygosity for loci on chromosome 17p in human malignant astrocytoma. *Cancer Res* 49:6572–6577
997. Fufts D, Pedone CA, Thomas GA, White R (1990) Allelotype of human malignant astrocytoma. *Can Res* 50:5784–5789

998. Fults D, Brockmeyer D, Tullous MW, Pedone CA, Cawthon RM (1992) p53 mutation and loss of heterozygosity on chromosomes 17 and 10 during human astrocytoma progression. *Cancer Res* 52:674–679
999. Fung K-M, Trojanowski JQ (1995) Animal models of medulloblastoma and related primitive neuroectodermal tumors. A review. *J Neuropathol Exp Neurol* 54:285–296
1000. Fung Y-KT, Murphree AL, T'Ang A, Qian J, Hinrichs SH, Benedict WF (1987) Structural evidence for the authenticity of the human retinoblastoma gene. *Science* 236:1657–1661
1001. Furlow LT (1960) The neurosurgical aspects of seventh nerve neurilemmoma. *J Neurosurg* 17:721–735
1002. Furtado D, Marques V (1946) Lipoma da cauda equina. *Cadern Cient* 1:127–132
1003. Furuta A, Takahashi H, Ikuta F, Onda K, Takeda N, Tanaka R (1992) Temporal lobe tumor demonstrating ganglioma and pleomorphic xanthoastrocytoma components. *J Neurosurg* 77:143–147
1004. Gabbai AA, Hochberg FH, Linggood RM, Bashir R, Hotleman K (1989) High-dose methotrexate for non-AIDS primary central nervous system lymphoma. Report of 13 cases. *J Neurosurg* 70:190–194
1005. Gabbiani G, Kapanci Y, Barazzzone P, Franke WW (1981) Immunochemical identification of intermediate-sized filaments in human neoplastic cells. A diagnostic aid for the surgical pathologists. *Am J Pathol* 104:206–216
1006. Gaffney CC, Sloane JP, Bradley NJ, Bloom HJG (1985) Primitive neuroectodermal tumors in the cerebrum. Pathology and treatment. *J Neurooncol* 3:23–33
1007. Gagel O (1938) Über Hirngeschwülste. *Z Neur* 161:69–113
1008. Gaist G, Piazza G (1959) Meningiomas in two members of the same family (with no evidence of neurofibromatosis) *J Neurosurg* 16:110–113
1009. Gajjar AJ, Heideman RL, Douglass EC, Kun LE, Kovnar EH, Sanford RA, Fairclough DL, Ayers D, Look AT (1993) Relation of tumor-cell ploidy to survival in children with medulloblastoma. *J Clin Oncol* 11:2211–2217
1010. Galatioto S, Gaddoni G (1971) Miosarcomi primitivi del SNC. *Acta Neurol (Napoli)* 26:297–302
1011. Gallager RL, Hellwig EB (1980) Neurothekeoma: a benign cutaneous tumor of nerve sheath origin. *Am J Clin Pathol* 74:759–766
1012. Gallatin WM, Weissman IL, Buchter EC (1983) A cell-surface molecule involved in organ-specific homing of lymphocytes. *Nature* 304:30–34
1013. Galli G, Galli-Kienle M, Cattabeni F, Fiecchi A, Grossi-Paoletti E, Paoletti R (1970) The sterol precursors of cholesterol in normal and tumor tissues. *Adv Enzyme Regul* 8:311–321
1014. Gallo V, Bertolotto A, Levi G (1987) The proteoglycan chondroitin sulfate is present in a subpopulation of cultured astrocytes and in their precursors. *Dev Biol* 123:282–285
1015. Gamblin GT, James P, Thomas J, Six E, Eil C (1985) Simulation of a prolactin-secretion adenoma by an intrasellar craniopharyngioma. *Neurosurgery* 16:689–692
1016. Gammarota U (1965) Rapporti tra malignità istopatologica clinica dei cordomi. *Arch Ital Patol Clin Tumori* 8:63–86
1017. Gandhour MS, Labourdette G, Vincendon G (1981) A biochemical and immunohistological study of S 100 protein in developing rat cerebellum. *Dev Neurosci* 4:98–103
1018. Gangemi M, Maiuri F, Fiorillo A, Migliorati R, Pettinati G, Del Giudice E (1987) Primary cerebral neuroblastomas. *Neurochirurgia* 30:48–52
1019. Gangji D, Reaman GH, Cohen SR, Bleyer WA, Ladisch S, Poplack DG (1980) Leukoencephalopathy and elevated levels of myelin basic protein in the cerebrospinal fluid of patients with acute lymphoblastic leukemia. *N Engl J Med* 1:19–21
1020. Ganong WF (1984) The brain renin-angiotensin system. *Ann Rev Physiol* 46:17–31
1021. Garcia DM, Fulling KH (1985) Juvenile pilocytic astrocytoma of the cerebrum in adults. *J Neurosurg* 63:382–386
1022. Garcia DM, Fulling KH, Marks JE (1985) The value of radiation therapy in addition to surgery for astrocytomas of the adult cerebrum. *Cancer* 55:919–927
1023. Garcia DM, Latifi HR, Simpson JR, Picker S (1989) Astrocytomas of the cerebellum in children. *J Neurosurg* 71:661–664
1024. Garcia DM, Marks JE, Latifi HR, Kliefoth Ab (1991) Childhood cerebellar astrocytomas: is there a role for postoperative irradiation? *Int J Radiat Oncol Biol Phys* 18:815–818

1025. Garcia JH, Okazaki H, Aronson SM (1963) Blood group frequencies and astrocytoma. *J Neurosurg* 20:397–399
1026. Gardner WJ, Frazier CH (1930) Bilateral acoustic neurofibromas: a clinical study and field survey of a family of five generations with bilateral deafness in thirty eight members. *Arch Neurol Psych* 23:266–302
1027. Garin-Chesa P, Beresdorf HR, Walker S, Rettig WS (1990) Immunohistochemical analysis of the A4 and AO10 (gp110) cell-surface antigens of human astrocytoma. *Am J Pathol* 136:797–807
1028. Garner TB, Curling O del, Kelly DL, Laster DW (1991) The natural history of intracranial venous angioma. *J Neurosurg* 75:715–722
1029. Garrett PG, Simpson WJK (1983) Ependymomas: results of radiation treatment. *Int J Radiat Oncol Biol Phys* 9:1121–1124
1030. Garrido E, Becker LE, Hoffman HJ, Heindrick EB, Humphreys R (1978) Gangliogliomas in children. A clinicopathological study. *Childs Brain* 4:339–346
1031. Garson JA, McIntyre PG, Kemshed JT (1985) N-myc amplification in malignant astrocytoma. *Lancet* 2:718–719
1032. Garson JA, Bourne SP, Allan PM, Leather C, Brownell DB, Coakham HB (1988) Immunohistological diagnosis of primary brain lymphoma using monoclonal antibodies: confirmation of B-cell origin. *Neuropathol Appl Neurobiol* 14:19–37
1033. Gärtner J (1957) Retinoblastom und Medulloblastom. Ein Vergleich ihres morphologischen und biologischen Verhaltens. *Gräfes Arch Ophtalm* 158:605–613
1034. Gass H, Van Wagenen WP (1950) Oligodendroglioma in pre-adolescence. Report of a case. *J Neurosurg* 7:374–376
1035. Gassel MM, Davies H (1961) Meningiomas in the lateral ventricles. *Brain* 84:605–627
1036. Gately MK, Glaser M, Dick SJ, Meitetal RW, Kornblith PL (1982) In vitro studies on cell-mediated immune response to human brain tumors. I Requirement of third party stimulator lymphocytes in the induction of cell mediated cytotoxic responses to allogeneic cultures of gliomas. *J Natl Cancer Inst* 69:1245–1254
1037. Gately S, Takano S, Brem S (1993) Immunohistochemical identification of plasminogen in human brain tumors. *Proc Am Assoc Cancer Res* 34:78
1038. Gatti RA, Swift M (1985) Ataxia-teleangiectasia. Genetics, neuropathology and immunology of a degenerative disease of childhood. Liss, New York
1039. Gay PC, Litchy WJ, Cascino TL (1987) Brain metastasis in hypernephroma. *J Neurooncol* 5:51–56
1040. Geisler N, Plessmann U, Weber K (1982) Related amino acid sequences in neurofilaments and non-neuronal intermediate filaments. *Nature* 296:448–450
1041. Geissinger JD, Bucy PC (1971) Astrocytomas of the cerebellum in children: long-term study. *Arch Neurol* 24:125–135
1042. Gennet IN, Cavenee WK (1990) Molecular genetics in the pathology and diagnosis of retinoblastoma. *Brain Pathol* 1:25–32
1043. Geraci JP, Spence AM (1979) RBE of cyclotron fast neutron for a rat brain tumor. *Radiat Res* 79:579–590
1044. Geran R, Congleton GF, Dudeck LE, Vendetti J, Abbott BJ, Gargus JL (1974) A mouse ependymoblastoma as an experimental model for screening potential antineoplastic drugs. *Cancer Chemother Rep* 4:53–87
1045. Gerdes J (1994) Immunohistochemical assesment of cell proliferation. *Brain Pathol* 4:298
1046. Gerdes J, Schwab U, Lemke H, Stein H (1983) Production of a mouse monoclonal antibody reactive with a human nuclear antigen associated with cell proliferation. *Int J Cancer* 31:13–20
1047. Gerdes J, Lamke H, Baisch H, Wacker H-H, Schwab U, Stein H (1984) Cell cycle analysis of a cell proliferation-associated human nuclear antigen defined by the monoclonal antibody Ki-67. *J Immunol* 133:1710–1715
1048. Germano I, Edwards MSB, Davis RL, Schiffer D (1994) Intracranial meningiomas of the first two decades of life. *J Neurosurg* 80:447–453
1049. Gerosa MA, Olivi A, Rosemblum ML, Semenzato GP, Pezzutto A (1982) Impaired immunocompetence in patients with malignant gliomas: the possible role of Tg-lymphocyte subpopulations. *Neurosurgery* 10:571–573

1050. Gerosa MA, Chilosi M, Iannucci A, Montagna M, Andrighetto GC, Stevanoni G, Tridente G (1984) Immunohistochemical characterization of Ia-DR positive cells in normal brain and gliomas. *J Neurooncol* 2:272
1051. Gerosa MA, Talarico D, Fognani C, Raimondi E, Colombatti M, Tridente G, De Carli L, Della Valle G (1989) Overexpression of n.ras oncogene and epidermal growth factor receptor gene in human glioblastomas. *J Natl Cancer Inst* 81:63–67
1052. Gerstner L, Jellinger K, Heiss WD, Wöber G (1977) Morphological changes in anaplastic gliomas treated with radiation and chemotherapy. *Acta Neurochir (Wien)* 36:117–138
1053. Gerweck LE, Kornblith PL, Burlett P, Wang J, Sureigert, S (1977) Radiation sensitivity of cultured brain human glioblastoma cells. *Radiology* 125:231–234
1054. Geschickter C, Copeland M (1949) Tumors of bone. Lippincot, Philadelphia
1055. Gessaga EC, Mair WGP, Grant DN (1973) Ultrastructure of a sacrococcygeal chordoma. *Acta Neuropathol (Berl)* 25:27–35
1056. Geuna E, Gori G (1962) Condroma della volta cranica. *Min Neurochir* 6:62–65
1057. Ghatak NR, Alexander E Jr (1977) Further observation on the fine structure of a colloid cyst of the third ventricle. *Acta Neuropathol (Berl)* 39:101–107
1058. Ghatak NR, McWhorter JM (1976) Ultrastructural evidence for CSF production by a choroid plexus papilloma. *J Neurosurg* 45:409–415
1059. Ghatak NR, Hirano A, Zimmerman HM (1971) Ultrastructure of a craniopharyngioma. *Cancer* 27:1465–1475
1060. Ghatak NR, Hirano A, Kasoff SS, Zimmerman HM (1974) Fine structure of an intracerebral epithelial cyst. *J Neurosurg* 41:75–82
1061. Gherardi R, Baudrimont M, Nguyen JP, Gaston A, Cesaro P, Degos JD, Caron JP, Poirier J (1986) Monstrocellular heavily lipidized malignant glioma. *Acta Neuropathol (Berl)* 69:28–32
1062. Ghim TT, Seo J-J, O'Brien M, Meackham L, Crocker I, Krawiecki N (1993) Childhood intracranial meningiomas after high-dose irradiation. *Cancer* 71:4091–4095
1063. Gi H, Nagao S, Yoshizumi H, Nishioka T, Uno J, Shingy T, Fujita Y (1990) Meningioma with hypergammaglobulinemia. *J Neurosurg* 73:628–629
1064. Giangaspero F (1989) Il medulloblastoma. *Quad Neuropat* 5:1–18
1065. Giangaspero F, Burger PC (1983) Correlations between cytologic composition and biological behavior in the glioblastoma multiforme: a postmortem study of 50 cases. *Cancer* 52:2320–2333
1066. Giangaspero F, Burger PC, Budwit DA, Usellini L, Mancini AM (1985) Regulatory peptides in neuronal neoplasms of the central nervous system. *Clin Neuropathol* 4:111–115
1067. Giangaspero F, Casadei GP, Burger PC (1987) Papillary craniopharyngioma. *Ital J Neurol Sci* 8:181
1068. Giangaspero F, Chieco P, Lisignoli G, Burger P (1987) Comparison of cytologic composition with microfluorometric DNA analysis of the glioblastoma multiforme and anaplastic astrocytoma. *Cancer* 60:59–65
1069. Giangaspero F, Doglioni C, Rivano MT, Piferi S, Gerdes J, Stein H (1987) Growth fraction in human brain tumors defined by the monoclonal antibody KI-67. *Acta Neuropathol (Berl)* 74:179–182
1070. Giangaspero F, Pession A, Trerè D, Badiali M, Galassi E, Ceccarelli C, Cavazzana A, Betts CM, Paolucci P, Stella M, Montaldi A (1991) Establishment of a human medulloblastoma cell line (BO-101) demonstrating skeletal muscle differentiation. *Tumori* 77:196–205
1071. Giani C, Finocchiaro G (1994) Mutation rate of the CDKN2 gene in malignant gliomas. *Cancer Res* 54:6338–6339
1072. Gill PS, Levine AM, Meyer PR, Boswell WD, Burkes RL, Parker JW, Hofman FM, Dworsky RL, Lukes RJ (1985) Primary central nervous system lymphoma in homosexual men: clinical, immunologic, and pathologic features. *Am J Med* 78:742–748
1073. Gilles FH, Winston K, Fulkiero A, Leviton A (1977) Histologic features and observational variation in cerebellar gliomas in children. *J Natl Cancer Inst* 58:175–181
1074. Gilles FH, Leviton A, Hedley-White ET, Jasnow M (1983) Childhood brain tumor update. *Human Pathol* 14:834–848
1075. Giombini S, Morello G (1978) Cavernous angiomas of the brain. Account of fourteen personal cases and review of the literature. *Acta Neurochir (Wien)* 40:61–82

1076. Giordana MT, Mauro A, Soffietti R, Leone M (1981) Association between multiple sclerosis and oligodendroglioma. *Ital J Neurol Sci* 2:403–409
1077. Giordana MT, Bertolotto A, Mauro A, Migheli A, Pezzotta S, Racagni D, Schiffer D (1982) Glycosaminoglycans in human cerebral tumors. Part III Histochemical findings and correlations. *Acta Neuropathol (Berl)* 57:299–305
1078. Giordana MT, Mauro A, Migheli A, Schiffer D (1983) Contribution of immunohistochemistry to the problem of differentiation in medulloblastomas. *Ital J Neurol Sci* 4:411–415
1079. Giordana MT, Germano I, Giaccone G, Mauro A, Migheli A, Schiffer D (1985) The distribution of laminin in human brain tumors: an immunohistochemical study. *Acta Neuropathol (Berl)* 67:51–57
1080. Giordana MT, Schiffer D, Mauro A, Migheli A (1986) Transplacental ENU tumors of the rat: Immunohistochemical contribution to the recognition of cell types. In: Walker MD, Thomas DGT (eds) *Biology of brain tumor*. Nijhoff, Boston, pp 121–129
1081. Giordana MT, Migheli A, Villare F, Schiffer D (1990) Radial glia in rats treated transplacentally by ENU. *J Neuropathol Exp Neurol* 49:273.
1082. Giordana MT, Cavalla P, Chiò A, Marino S, Vigliani MC, Schiffer D (1993) Usefulness of Ki-67, clone MIB.1 as a prognostic factor in ependymomas. *J Neuropathol Exp Neurol* 52:324
- 1082a. Giordana MT, Cavalla P, Chiò A, Marino S, Soffietti R, Vigliani MC, Schiffer D. (1995) Prognostic factors in adult medulloblastoma. A clinico-pathologic study. *Tumori* 81:338–346
1083. Giordana MT, Cavalla P, Dutto A, Borsotti L, Chiò A, Schiffer D (1996) Is medulloblastoma the same tumor in children and adult? *J Neurooncol* (in press)
1084. Girgah N, Ackerley CA, Moscarello MA (1991) Localization of CD44 (P80) on the external surface of a human astrocytoma cell. *Neuroreport* 2:441–444
1085. Giuffrè R (1986) Intradural spinal lipomas: review of the literature (99 cases) and report of an additional case. *Acta Neurochir (Wien)* 14:69–95
1086. Giuffrè R, Di Lorenzo N (1975) Evolution of a primary intrasellar germinomatous teratoma into a choriocarcinoma. *J Neurosurg* 42:602–604
1087. Giuffrè R, Gagliardi FM (1968) Unusual hypophyseal tumour of Rathke's cleft origin. *Neurochirurgia* 11:81–89
1088. Giuffrè R, Liccardo G, Pastore FS, Spallone A, Vagnozzi R (1990) Potential risk factors for brain tumors in children. *Childs Nerv Syst* 6:8–12
1089. Gjerris F, Klinken L (1978) Long-term prognosis in children with benign cerebellar astrocytoma. *J Neurosurg* 49:178–184
1090. Glantz MJ, Burger PC, Friedman AH, Radtke RA, Massey EW, Schold SC (1994) Treatment of radiation-induced nervous system injury with heparin and warfarin. *Neurology* 44:2020–2027
1091. Glaser BM, D'Amore PA, Michels RG, Patz A, Fenselau A (1980) Demonstration of vasoproliferative activity from mammalian retina *J Cell Biol* 84:298–304
1092. Glass JP, Hwang TL, Leavens ML, Libshitz HI (1984) Cerebral radiation necrosis following treatment of extracranial malignancies. *Cancer* 54:1966–1972
1093. Glauser TA, Packer RJ (1991) Cognitive deficits in long-term survivors of childhood brain tumors. *Childs Nerv Syst* 7:2–12
1094. Glenn GM, Linehan WM, Hosoe S, Latif F, Yao M, Choike P, Gorin MB, Chew E, Oldfield EA, Manolatos C, Orcutt ML, Walther MM, Weiss GH, Tory K, Jensson O, Lerman MI, Zbar B (1992) Screening for von Hippel-Lindau disease by DNA polymorphism analysis. *J Am Med Ass* 267:1226–1231
1095. Glenner GG, Grimley PM (1974) Tumors of the extra-adrenal paraganglion systems (including chemoreceptors). *Atlas of tumor pathology*, 2nd series, vol 9. AFIP, Washington
1096. Glick RP, Gittleman R, Patel K, Laksmman R, Tsibris JCM (1989) Insulin and insulin-like growth factor I in brain tumors: binding and in vitro effects. *Neurosurgery* 24:791–97
1097. Glimelius B, Norling B, Westermarck B, Wasteson A (1978) Composition and distribution of glycosaminoglycans in cultures of human normal and malignant glial cells. *Biochem J* 172:443–456
1098. Globus JH (1932) Malformations in the central nervous system. In: Penfield W (ed) *Cytology and cellular pathology of the nervous system*. Hoeffer, New York
1099. Globus JH (1937) Meningiomas. Origin, divergence in structure and relationship to contiguous tissues in light of phylogenesis and ontogenesis of the meninges, with suggestion of a simplified classification of meningeal neoplasms. *Arch Neurol Psychiatr* 38:667–712

1100. Globus JH, Cares RM (1953) Neuroepithelioma. Its place in the histogenetic classification of primary neuroectodermal brain tumors. *J Neuropathol Exp Neurol* 12:311–348
1101. Globus JH, Kuhlenbeck H (1944) The subependymal cell plate (matrix) and its relationship to brain tumours of the ependymal type. *J Neuropathol Exp Neurol* 3:1–35
1102. Globus JH, Strauss I (1925) Spongioblastoma multiforme. *Arch Neurol* 14:139–151
1103. Gluszczyk A (1962) A cancer arising in a dermoid of the brain. *J Neuropathol Exp Neurol* 21:383–387
1104. Gnarr JR, Tory K, Weng Y, Schmidt L, Wei MH, Li H, Latif F, Liu S, Chen F, Duh FM, Lubensky L, Duan DR, Florence C, Pozzatti R, Walther MM, Bander NH, Grossman HB, Brauch H, Pomer S, Brooks JD, Isaacs WB, Lerman MI, Zbar B, Lineham WM (1994) Mutation of the VHL tumour suppressor gene in renal carcinoma. *Nat Genet* 7:85–90
1105. Go KG, Wilmink JT, Molenaar H (1988) Peritumoral brain edema associated with meningiomas. *Neurosurgery* 23:175–179
1106. Goates JJ, Dickson DW, Horonpian DS (1991) Meningiomatosis: an immunohistochemical study. *Acta Neuropathol (Berl)* 82:527–532
1107. Godwin JT (1959) Subependymal glomerate astrocytoma. Report of two cases. *J Neurosurg* 16:385–389
1108. Goebel HH, Cravioto H (1972) Ultrastructure of human and experimental ependymomas: a comparative study. *J Neuropathol Exp Neurol* 31:54–71
1109. Goebel HH, Shimokawa K, Schaake TH, Kremp A (1979) Schwannoma of the sellar region. *Acta Neurochir (Wien)* 48:191–197
1110. Gol A (1961) The relatively benign astrocytomas of the cerebrum. A clinical study of 194 verified cases. *J Neurosurg* 61:895–900
1111. Gol A, McKissock W (1959) The cerebellar astrocytomas. A report on 98 verified cases. *J Neurosurg* 16:287–296
1112. Gold EB, Gordis L (1979) Patterns of incidence of brain tumors in children. *Ann Neurol* 5:565–568
1113. Gold EB, Gordis L, Tonascia J, Szklo M (1978) Increased risk of brain tumors in children exposed to barbiturates. *J Natl Cancer Inst* 61:1031–1034
1114. Gold EB, Gordis L, Tonascia J, Szklo M (1979) Risk factors for brain tumors in children. *Am J Epidemiol* 109:309–318
1115. Gold EB, Diener MD, Szklo M (1982) Parental occupations and cancer in children: a case-control study and review of the methodologic issues. *J Occup Med* 24:578–584
1116. Gold EB, Leviton A, Lopez R, Austin DF, Gilles FM, Hedley-White ET, Kolonel L, Lyon JL, Swanson GM, Weiss NS, West DW, Aschenbrener C (1994) The role of family history in risk of childhood brain tumors. *Cancer* 73:1302–1311
1117. Goldberg GM, Eshbaugh DE (1960) Squamous cell nests of the pituitary gland as related to the origin of craniopharyngiomas: a study of the presence in the newborn and infants up to age four. *Arch Pathol* 70:293–299
1118. Goldberg ID, Kurland LT (1962) Mortality in 33 countries from diseases of the nervous system. *World Neurol* 3:444–465
1119. Goldberg-Stern H, Gadoth N, Stern S, Cohen JJ, Zaizov R, Sandbank U (1991) The prognostic significance of glial fibrillary acidic protein staining in medulloblastoma. *Cancer* 68:568–573
1120. Goldgar DE, Green P, Parry DM, Mulvihill JJ (1989) Multipoint linkage analysis in neurofibromatosis type I: an international collaboration. *Am J Hum Genet* 44:6–12
1121. Goldhaber MK, Selby JV, Hiatt RA, Quesenberry CP (1990) Exposure to barbiturate in utero and during childhood and risk of intracranial and spinal cord tumors. *Cancer Res* 50:4600–4603
1122. Goldhammer D, Goebel HH (1980) Dense core vesicles in the desmoplastic variant of cerebral neuroblastoma. *Acta Neuropathol (Berl)* 50:81–83
1123. Goldman JE (1995) Lineage, migration and fate determination of postnatal subventricular zone cells in the mammalian CNS. *J Neurooncol* 24:61–64
1124. Goldman RL (1969) Gliomyosarcoma of the cerebrum. *Am J Clin Pathol* 52:741–744
1125. Goldstein JD, Dickson DW, Moser FG, Hirschfeld AD, Freeman K, Llena JF, Kaplan B, Davis L (1990) Primary central nervous system lymphoma in acquired immune deficiency syndrome. *Cancer* 67:2756–2765

1126. Goldstein SJ, Wilson D, Young AB, Guidry GJ (1983) Craniopharyngioma intrinsic to the third ventricle. *Surg Neurol* 20:249–253
1127. Goldwein JW (1987) Radiation myelopathy: a review. *Med Ped Oncol* 15:89–95
1128. Goldwein JW, Leahy JM, Packer RJ, Sutton LN, Curran WJ, Rorke LB, Schut L, Littman PS, D'Angio GJ (1988) Intracranial ependymomas in children. *Pediatr Neurosci* 14:149 (abstr)
1129. Goldwein JW, Corn BW, Finlay JL, Packer RJ, Rorke LB, Schut L (1991) Is craniospinal irradiation required to cure children with malignant (anaplastic) intracranial ependymomas? *Cancer* 15:2766–2771
1130. Gomez JC, Garcia JH, Colon LE (1985) A variant of cerebral glioma called pleomorphic xanthoastrocytoma: case report. *Neurosurgery* 16:703–707
1131. Gomez MR (1979) Tuberous sclerosis. Raven, New York
1132. Gonatas NK, Besen M (1963) An electron microscopic study of three human psammomatous meningiomas. *J Neuropathol Exp Neurol* 22:263–273
1133. Gonzales DG, Schuster-Uitterhoere ALJ (1983) Primary non-Hodgkin's lymphoma of the central nervous system. Results of radiotherapy in 15 cases. *Cancer* 51:2048–2052
1134. Gonzales-Crussi F (1982) Extragenital teratomas. In: Atlas of tumor pathology, 2nd series, fascicle 18. AFIP, Washington
1135. Gonzalez-Vitale JC, Garcia-Bunuel R (1976) Meningeal carcinomatosis. *Cancer* 37:2906–2911
1136. Gonzalez-Vitale JC, Slavin RE, McQuenn DJ (1976) Radiation induced intracranial malignant fibrous histiocytoma. *Cancer* 37:2960–2963
1137. Goodman R, Bassett CAL, Henderson AS (1983) Pulsing electromagnetic fields induce cellular transcription. *Science* 220:1283–1285
1138. Goodrich JT, Post KD, Duffy P (1985) Ciliated craniopharyngioma. *Surg Neurol* 24:105–111
1139. Goth R, Rajewski M (1974) Persistence of 0<sup>6</sup>-ethylguanine in rat brain DNA. Correlation with nervous system specific carcinogenesis by ethylnitrosourea. *Proc Natl Acad Sci USA* 71:639–653
1140. Gottschalk J, Villagran R, Conzen M, Schnabel R (1989) Meningiomas with hyaline bodies (pseudopsammoma bodies). Seven new cases and review of the literature. *Clin Neuropathol* 8:232
1141. Gottschalk J, Korves M, Skotzek-Konrad B, Goebel H, Cervos-Navarro J (1993) Dysembryoplastic neuroepithelial micro-tumor in a 75 year old patient with long-standing epilepsy. *Clin Neuropathol* 12:175–178
1142. Gould VE (1986) Histogenesis and differentiation: a reevaluation of these concepts as criteria for the classification of tumors. *Hum Pathol* 17:212–215
1143. Gould VE, Moll R, Moll I, Lee I, Schwechheimer K, Franke WW (1986) The intermediate filament complement of the spectrum of nerve sheath neoplasms. *Lab Invest* 55:463–475
1144. Gould VE, Lee I, Wiedemann B, Mole R, Chejfec G, Franke WW (1986) Synaptophysin: A novel marker for neurons, certain neuroendocrine cells, and their neoplasms. *Hum Pathol* 17:979–983
1145. Gould VE, Rorke LB, Jansson DS, Molenaar WM, Trojanowski JQ, Lee VMY, Parker RJ, Franke WW (1990) Primitive neuroectodermal tumors of the central nervous system express neuroendocrine markers and may express all classes of intermediate filaments. *Hum Pathol* 21:245–252
1146. Gouliarnos AD, Jimenez JP, Goree JA (1978) Computed tomography and skull radiography in the diagnosis of calcified brain tumor. *Am J Roentgenol* 130:761–764
1147. Goutelle A, Fisher G (1977) Les épendymomes, intracranien et intrarachidiens. *Neurochirurgie* 23 [Suppl]:1
1148. Gowers WR (1876) Myo-lipoma of the spinal cord. *Trans Pathol Soc (London)* 27:19–43
1149. Gown AM, Gabbiani G (1984) Intermediate-sized (10 nm) filaments in human tumors. In De Lellis RA (ed) *Advances in immunohistochemistry*. Masson, New York, pp 89–109
1150. Grady EF, Schwab M, Rosenau W (1987) Expression of N-myc and C-src during the development of fetal human brain. *Cancer Res* 47:2931–2936
1151. Graf CJ, Perret GE, Torner JC (1983) Bleeding from cerebral arteriovenous malformations as part of their natural history. *J Neurosurg* 58:331–337
1152. Grant FC (1956) A study of the results of surgical treatment in 2326 consecutive patients with brain tumor. *J Neurosurg* 13:479–488

1153. Grant JW, Callagher PJ (1986) Pleomorphic xanthoastrocytoma. Immunohistochemical methods for differentiation from fibrous histiocytomas with similar morphology. *Am J Surg Pathol* 10:336–341
1154. Grant JW, Kaech D, Jones DB (1986) Spinal cord compression as the first presentation of lymphoma – a review of 15 cases. *Histopathology* 10:1191–1202
1155. Grant JW, Steart PV, Aguzzi A, Jones DB, Gallagher PJ (1989) Gliosarcoma: an immunohistochemical study. *Acta Neuropathol (Berl)* 79:305–309
1156. Grattarola FR (1955) Emangioblastomi dell'encefalo. (*Studio clinico ed anatomico-patologico*). *Cancro* 1:3–14
1157. Gratzner HG (1982) Monoclonal antibody of 5-bromo- and 5-iododeoxyuridine: a new reagent for detection of DNA replication. *Science* 218:474–475
1158. Gray SW, Singhabhandhu B, Smith RA, Skandalakis JE (1975) Sacrococcygeal chordoma. Report of a case and review of the literature. *Surgery* 78:573–582
1159. Grcevic N, Yates PO (1957) Rosenthal fibres in tumours of the central nervous system. *J Pathol Bact* 73:467–472
1160. Greaves MF, Verbi W, Kennett R (1980) A monoclonal antibody identifying a cell surface antigen shared by common acute lymphoblastic leukemias and B lineage cell. *Blood* 56:1141–1144
1161. Green AJ, Smith M, Yates JRW (1994) Loss of heterozygosity on chromosome 16p13 in hamartomas from tuberous sclerosis patients. *Nature Genet* 6:193–196
1162. Greenberg HS, Chalder WF, Diaz RF, Ensinger WD, Junck L, Page MA, Gebarski SS, McKeever P, Hood TW, Stetson PL, Litcher AS, Tankanow R (1988) Intra-arterial bromodeoxyuridine radiosensitization and radiation in treatment of malignant astrocytomas. *J Neurosurg* 69:500–505
1163. Greenblatt M, Shubik P (1968) Tumor angiogenesis: transfilter diffusion studies in the hamster by the transtarent chamber technique. *J Natl Cancer Inst USA* 41:111–124
1164. Greene RC (1951) Extraventricular and intra-cerebellar papilloma of the choroid plexus. *J Neuropathol Exp Neurol* 10:204–207
1165. Greig N (1987) Optimizing drug delivery to brain tumors. *Cancer Treat Rev* 14:1–28
1166. Greig N, Sweney D (1986) Drug delivery to the brain by blood-brain barrier circumvention and drug modification. In: Neuwelt E (ed) *The clinical impact of the blood-brain barrier and its manipulation*. Plenum, New York
1167. Griepentrog F, Pauly H (1957) Intra- und extrakranielle frühmanifeste Medulloblastome bei erbgleichen Zwillingen. *Zbl Neurochir* 17:129–140
1168. Griesser H (1993) Applied molecular genetics in the diagnosis of malignant non-Hodgkin's lymphoma. *Diagn Mol Pathol* 2:177–191
1169. Griffin CA, Hawkins AL, Packer RJ, Rorke LB, Emanuel BS (1988) Chromosome abnormalities in pediatric brain tumors. *Cancer Res* 48:175–180
1170. Griffin CA, Long PP, Carson BS, Brem H (1992) Chromosome abnormalities in low-grade central nervous system tumors. *Cancer Genet Cytogenet* 60:67–73
1171. Grigsby PW, Stokes S, Marks JE, Simpson JR (1988) Prognostic factors and results of radiotherapy alone in the management of pituitary adenomas. *Int J Radiation Oncol Biol Phys* 15:1103–1110
1172. Groeshammer T, Zimmer C, Vogeley KT (1991) Immunohistochemistry of primitive neuroectodermal tumors in infants with special emphasis on cytokeratin expression. *Acta Neuropathol (Berl)* 82:494–501
1173. Groothuis DR, Vick NA (1980) Radionecrosis of the central nervous system: the perspective of the clinical neurologist and neuropathologist. In: Gilbert HA, Kagan AR (eds) *Radiation damage to the nervous system*. Raven, New York, pp 93–106
1174. Groothuis DR, Fisher JM, Vick NA (1980) Experimental gliomas: an autoradiographic study of the endothelial component. *Neurology* 30:297–301
1175. Groothuis DR, Warkne PC, Molnar P, Lapin G, Miklael M (1990) Effect of hyperosmotic blood-brain barrier disruption on transcapillary transport in canine brain tumors. *J Neurosurg* 72:441–449
1176. Grossi-Paoletti E, Paoletti P, Schiffer D, Fabiani A (1970) Experimental brain tumors induced in rats by nitrosoethylurea derivatives. Part 2: Morphological aspects of nitrosoethylurea tumours obtained by transplacental induction. *J Neurol Sci* 11:573–581



1177. Grossman SA (1995) Research approaches of the NABTT CNS Consortium. In: Abstract 11th International Conference of Brain Tumor Research and Therapy, Silverado 1995
1178. Grover WD, Rorke LB (1968) Invasive craniopharyngioma. *J Neurol Neurosurg Psychiatry* 31:580–582
1179. Grunberg SM (1991) The role of progesterone receptors in meningioma. In Muggia FM (ed) *New drugs, concepts and results in cancer chemotherapy*. Kluwer, Boston, pp 127–137
1180. Grunert V, Horcajada J, Sunder-Plassmann M (1970) Familial occurrence of intracranial meningiomas. *Wien Med Wochenschr* 120:807–808
1181. Grynfeldt E (1926) Etude d'histopathologie expérimentale sur la dégénérescence muqueuse de la névroglie. *Congr Ass Anat 21ème Réun* 29
1182. Guarda LG, Ordonez NG, Smith JL, Hanssen G (1982) Immunoperoxidase localization of Factor VIII in angiosarcomas. *Arch Pathol Lab Med* 106:515–516
1183. Gudeman SK, Sullivan HG, Rosner MJ, Becker DP (1979) Surgical removal of bilateral papillomas of the choroid plexus of the lateral ventricles with resolution of hydrocephalus: case report. *J Neurosurg* 50:677–681
1184. Gudmundsson KR (1970) A survey of tumours of the central nervous system in Iceland during the 10-year period 1954–1963. *Acta Neurol Scand* 46:538–552
1185. Guha A, Resch L, Tator CH (1989) Subependymoma of the thoracolumbar cord. Case report. *J Neurosurg* 71:781–787
1186. Guha A, Dashner K, Black PMCL, Wagner JA, Stiles CD (1995) Expression of PDGF and PDGF receptors in human astrocytoma operation specimens supports the existence of an autocrine loop. *Int J Cancer* 60:168–173
1187. Guidetti B, Fortuna A, Moscatelli G, Riccio A (1964) I tumori intramidollari. *Lav Neuropsichiatri* 35:1–409
1188. Gullotta F (1958) Papilloma bilaterale dei plessi coroidei. *Arch Ital Patol Clin Tumori* 2:316–328
1189. Gullotta F (1964) Zur in vitro-Diagnostik gliös-mesenchymaler Mischgeschwülste. *Dtsch Ztschr Nervenheilkd* 186:323–335
1190. Gullotta F (1965) La genesi formale delle fibre di Rosenthal. *Acta Neurol (Napoli)* 20:704–711
1191. Gullotta F (1967) Das sogenannte Medulloblastom. Springer, Berlin Göttingen Heidelberg
1192. Gullotta F (1971) Kleinhirngeschwülste des Kindesalters (eine vergleichende elektronen-optische und Gewebekulturuntersuchung). *Verh Dtsch Ges Path* 55:315
1193. Gullotta F, Fliehdner E (1972) Spongioblastomas, astrocytomas and Rosenthal fibres: ultrastructural, tissue culture and enzyme histochemical investigations. *Acta Neuropathol (Berl)* 22:68–78
1194. Gullotta F, Kreutzberg GW (1963) Das Gliom des Opticus. Morphologische und histochemische Untersuchungen am Schnittpreparat und der Gewebekultur. *Acta Neuropathol (Berl)* 2:413–424
1195. Gullotta F, Mazzoleni G, Rubbiani U (1958) Considerazioni anatomo-cliniche sui neurinomi del plesso brachiale. *Arch Ital Patol Clin Tumori* 2:925–947
1196. Gullotta F, Schindler F, Schmutzler R, Weeks-Seifert A (1983) GFAP in brain tumor diagnosis: possibilities and limitations. *Pathol Res Pract* 178:129–135
1197. Gunthel C, Ng V, McGrath M, Herndier B, Shiramizu B (1994) Association of Epstein-Barr virus types 1 and 2 with acquired immunodeficiency syndrome-related primary central nervous system lymphomas. *Blood* 618–619
1198. Günthert U, Hofmann M, Rudy W, Reber S, Zoller M, Haussmann I, Matzku S, Wenzel A, Ponta H, Herrlich P (1991) A new variant of glycoprotein CD44 confers metastatic potential to rat carcinoma cells. *Cells* 65:13–24
1199. Gusek W (1962) Submikroskopische Untersuchungen als Beitrag zur Struktur und Onkologie der "Meningeome". *Beitr Pathol Anat* 127:274–326
1200. Guseo A, Boldizar F, Gellert M (1975) Elektronmikroskopische Untersuchungen bei striodentaler Kalzifikation (Fahr). *Acta Neuropathol (Berl)* 31:305–313
1201. Guthrie BL, Ebersold MJ, Scheithauer BW, Shaw EG (1989) Meningeal hemangiopericytoma: histopathological features, treatment, and long-term follow-up of 44 cases. *Neurosurgery* 25:514–522
1202. Gutin PH, Wilson CB (1990) Radiosurgery for malignant brain tumors. *J Clin Oncol* 4:571–573

1203. Gutin PH, Hilton J, Fein VJ, Allen AE, Walker MD (1977) S<sub>1</sub> nuclease from *Aspergillus oryzae* for the detection of DNA damage and repair in the gamma-irradiated intracerebral rat gliosarcoma 9L. *Radiat Res* 72:100–106
1204. Gutin PH, Bernstein M, Sano J (1984) Combination therapy with 1,3-bis(2-chloroethyl)-1-nitrosourea and low dose rate radiation in the 9L rat brain tumor and spheroid models: implications for brain tumor brachytherapy. *Neurosurgery* 15:781–786
1205. Gutin PH, Leibel SA, Sheline GE (1991) Radiation injury to the nervous system. Raven, New York
1206. Gutmann DH, Wood DL, Collins FS (1991) Identification of the neurofibromatosis type 1 gene product. *Proc Natl Acad Sci USA* 88:9658–9662
1207. Haapasalo H, Isola J, Sallinen P, Kalimo H, Helin H, Rantala I (1993) Aberrant p53 expression in astrocytic neoplasms of the brain: association with proliferation. *Am J Pathol* 142:1347–1351
1208. Haddad P, Thaell JF, Kiely JM, Harrison EG Jr, Miller RH (1976) Lymphoma of the spinal extradural space. *Cancer* 38:1862–1866
1209. Haddad SF, Meneses AH, Bell WE, Godersky JC, Afifi AK, Bele JF (1991) Brain tumors occurring before 1 year of age: a retrospective review of 22 cases in an 11-year period (1977–1987). *Neurosurgery*, 29:8–13
1210. Haddad SF, Moore SA, Schelper RL, Goeken J (1991b) Smooth muscle cells can comprise the sarcomatous component of gliosarcoma. *J Neuropathol Exp Neurol* 50:291
- 1210a. Haddad SF, Moore SA, Schelper RL, Goeken JA (1992) Vascular smooth muscle hyperplasia underlies the formation of glomeruloid vascular structures of glioblastoma multiforme. *J Neuropathol Exp Neurol* 51:488–492
1211. Hadfield MG, Silverberg SG (1972) Light and electron microscopy of giant-cell glioblastoma. *Cancer* 30:989–996
1212. Hadfield MG, Ghatak NR, Wanger GP (1985) Xanthogranulomatous colloid cyst of the third ventricle. *Acta Neuropathol (Berl)* 66:343–346
1213. Haenszel W, Marcus SC, Zimmerer EG (1956) Cancer morbidity in urban and rural Iowa. US Dept of public health monography, US Government printing office, Washington, no 37, pp 1–6, 55, 60, 63, 81
1214. Haglid K, Carlsson CA, Thulin CA (1970) Lactate dehydrogenase isoenzymes and proteins in human gliomas. *Neurochirurgia* 13:19–28
1215. Haglid K, Carlsson CA, Stavrou D (1973) An immunological study of human brain tumors concerning the brain specific proteins S-100 and 14.3.2. *Acta Neuropathol (Berl)* 24:187–196
1216. Haimoto H, Takahashi Y, Koshikawa T, Nagura H, Kato K (1985) Immunohistochemical localization of gamma-enolase in normal human tissue other than nervous and neuroendocrine tissue. *Lab Invest* 52:257–263
1217. Hajdu SI (1979) Pathology of soft tissue tumors. Lea and Febiger, Philadelphia
1218. Hajós F, Bascó E (1984) The surface-contact glia. *Adv Anat Embryol Cell Biol* vol 84, Springer, Berlin Heidelberg New York
1219. Hakuba A, Hashi K, Fujita K, Ikuno A, Nakamura T, Inoue Y (1979) Jugular foramen neurinomas. *Surg Neurol* 11:83–94
1220. Halberg FE, Wara WM, Filippin LF, Fowards MSB, Levin VA, Davis RL, Prados MB, Wilson CB (1991) Low-dose craniospinal radiation therapy for medulloblastoma. *Int J Rad Oncol Biol Phys* 20:651–654
1221. Hall EJ (1988) Radiobiology for the radiologist. Lippincott, Philadelphia
1222. Hall PA, Levison DA, Woods AL, Yu CC-W, Kellock DB, Watkins JA, Barnes DL, Gillett CE, Camplejohn R, Dover R, Waseem NH, Lane DP (1990) Proliferating cell nuclear antigen (PCNA) immunolocalization in paraffin sections: an index of cell proliferation with evidence of deregulated expression in some neoplasm. *J Pathol* 162:285–294
1223. Hall WA, Fodstad O (1992) Immunotoxins and central nervous system neoplasia. Review article. *J Neurosurg* 76:1–12
1224. Hall WA, Djalilian HR, Sperduto PW, Cho KH, Gerbi BJ, Gibbons JP, Rohr M, Clark HB (1995) Stereotactic radiosurgery for recurrent malignant gliomas. *J Clin Oncol* 13:1642–1648
1225. Hallervorden J (1959) Ueber die Hamartome (Ganglioneurome) des Kleinhirns. *Dtsch Ztschr Nervenheilkd* 179:531–563

1226. Halmagyi GM, Evans WA (1978) Lipoma of the quadrigeminal plate causing progressive hydrocephalus: case report. *J Neurosurg* 49:453–456
1227. Halper J, Scheithauer BW, Okaraki H, Laws ER (1986) Meningio-angiomatosis: a report of six cases with special reference to the occurrence of neurofibrillary tangles. *J Neuropathol Exp Neurol* 45:426–446
1228. Halper J, Colvard DS, Scheithauer BW, Jiang N-S, Press MF, Grahah ML, Riehl E, Laws ER Jr, Spelsberg TC (1989) Estrogen and progesterone receptors in meningiomas: comparison of nuclear finding, dextran-coated charcoal, and immunoperoxidase staining assays. *Neurosurgery* 25:546–553
1229. Halperin EC, Bentel G, Heinz ER, Burger PC (1989) Radiation therapy treatment planning in supratentorial glioblastoma multiforme: an analysis based on post mortem topographic anatomy with CT correlation. *Int J Radiat Oncol Biol Phys* 17:1347–1350
1230. Hamilton AE, Rubinstein LJ, Poole GJ (1973) Primary intracranial esthesioneuroblastoma (olfactory neuroblastoma). *J Neurosurg* 38:548–556
1231. Hamilton SR, Liu B, Parsons RE, Papadopoulos N, Jen J, Powell SM, Krush AJ, Berk T, Cohen Z, Tetu B, Burger TC, Wood PA, Taqi F, Booker SV, Petersen GM, Offerhaus GJA, Tersmette AC, Giardiello FM, Vogelstein B, Kinzler KW (1995) The molecular basis of Turcot's syndrome. *New Eng J Med* 332:839–847
1232. Hamilton WJ, Mossman HW (1972) Human embryology. Prenatal development of form and function. Williams and Wilkins, Baltimore, pp 54–82
1233. Hamperl H (1964) The nomenclature of tumours of nervous system. In: Zülch KJ, Woolf AL (eds) Classification of brain tumours. *Acta Neurochir (Wien)* [Suppl] 10:5–7
1234. Hanefeld F (1967) Histochemische Untersuchungen zur Verteilung und Aktivität hydrolytischer Enzyme in Gliomen. *Dtsch Ztschr Nervenheilkd* 192:165–173
1235. Hanjan SNS, Kearney JF, Cooper MD (1982) A monoclonal antibody (MMA) that identifies a differentiation antigen on human myelomonocytic cells. *Clin Immunol Immunopathol* 23:172–188
1236. Hardy M, Crowe SJ (1936) Early asymptomatic acoustic tumor: report of 6 cases. *Arch Surg* 32:292–306
1237. Harik SI, Sutton CH (1979) Putrescine as a biochemical marker of malignant brain tumors. *Cancer Res* 39:5010–5015
1238. Harnanine-Singh D, Geddes G, Hyde JB (1972) Size and number of arteries and veins in normal human neopallium. *J Anat* 11:171–179
1239. Harper CG, Stewart-Wynne EG (1978) Malignant optic gliomas in adults. *Arch Neurol* 35:731–735
1240. Harriman DGF (1958) An intraspinal enterogenous cyst. *J Pathol Bacteriol* 75:413–419
1241. Harrington JM, Oakes D (1984) Mortality study of british pathologists, 1974–1980. *Br J Ind Med* 41:188–191
1242. Harris JR, Levene MB (1976) Visual complications following irradiation for pituitary adenomas and craniopharyngiomas. *Radiology* 120:167–171
1243. Harris M (1980) The ultrastructure of benign and malignant fibrous histiocytomas. *Histopathology* 4:29–44
1244. Harris M, Moore IE, Steart PV, Weller RO (1990) Protein gene product (PGP) 9.5 as a reliable marker in primitive neuroectodermal tumours – an immunohistochemical study of 21 childhood cases. *Histopathology* 16:271–277
1245. Harris N, Jeffe E, Stein H, Banks P, Chan J, Cleary M, Deisler G, Wolf-Peters C, Falini B, Gatter K, Grogan T, Isaacson P, Knowles D, Mason D, Muller-Hermelink H, Pileri S, Piris M, Ralfklaer E, Warnke R (1994) A revised European-American classification of lymphoid neoplasm: a proposal from the international lymphoma study group. *Blood* 84:1361–1392
1246. Harrison JD, Rose PE (1985) Myxoid meningioma: histochemistry and electron microscopy. *Acta Neuropathol (Berl)* 68:80–82
1247. Harrison MJ, Morgello S, Post KD (1994) Epithelial cystic lesions of the sellar and parasellar region: a continuum of ectodermal derivations? *J Neurosurg* 80:1018–1025
1248. Harsh GR, Levin VA, Gutin PH, Seager M, Silver P, Wilson CB (1987) Reoperation for recurrent glioblastoma and anaplastic astrocytoma. *Neurosurgery* 21:615–621

1249. Hart MN, Earle KM (1973) Primitive neuroectodermal tumors of the brain in children. *Cancer* 32:890–897
1250. Hart MN, Petito CK, Earle KM (1974) Mixed gliomas. *Cancer* 33:134–140
1251. Hasegawa H, Ushio I, Mori M et al (1974) Primary intracranial choriocarcinoma in the pineal region. *Med J Osaka Univ* 25:63–71
1252. Hasagawa H, Bitoh S, Koshino K, Obashi J, Kabayashi Y (1991) Dysembryoplastic neuroepithelial tumor. A case report. *Neurol Surg* 19:553–557
1253. Hasenjäger Th (1939) Über die Ependymitis blastomatosa bei Ventrikelnahen Gliomen. *Arch Psych Nervenkrankh* 110:605–632
1254. Hassoun J (1989) Pinealomas: need for an ultrastructural diagnosis. In: Fields WS (ed) *Primary brain tumors. A review of histologic classifications*. Springer, Berlin Heidelberg New York, pp 82–85
1255. Hassoun J (1989b) General discussion of part one. In: Fields WS (ed) *Primary brain tumors. A review of histologic classification*. Springer, Berlin Heidelberg New York, p 108
1256. Hassoun J, Gambarelli D, Choux M, Toga M (1980) Macrophagic activity in intracerebral germinoma: ultrastructural study of a case. *Hum Pathol* 11:207–210
1257. Hassoun J, Andrac L, Gambarelli D, Toga M (1981) Lymphomes malins primitifs du système nerveux central. Etude anatomoclinique, ultrastructurale et immunocytoclinique. A propos de 23 cas. *Ann Pathol* 1:193–203
1258. Hassoun J, Gambarelli D, Grisoli F, Pellet W, Salamon G, Pellissier JF, Toga M (1982) Central neurocytoma. An electron microscopic study of two cases. *Acta Neuropathol (Berl)* 56:151–156
1259. Hassoun J, Gambarelli D, Peragut JC, Toga M (1983) Specific ultrastructural markers of human pinealomas: a study of four cases. *Acta Neuropathol (Berl)* 62:31–40
1260. Hassoun J, Figarella-Branger D, Gambarelli D (1990) Central neurocytomas. *Biwako Symposium on Brain Tumor Pathology*. 9–10 September, Siwako, Japan, p 37
1261. Hattori T, Fujita S (1974) Scanning electron microscopic study on morphology of matrix cells, and on development and migration of neuroblasts in human and chick embryo. *J Electronmicroscopy* 23:269–276
1262. Hatva E, Kaipainen A, Mentula P, Jääskeläinen J, Paetau A, Haltia M, Alitalo K (1995) Expression of endothelial cell-specific receptor tyrosine kinases and growth factors in human brain tumors. *Am J Pathol* 146:368–378
1263. Haugen Å, Laerum OD (1978) Scanning electron microscope of neoplastic neurogenic rat cell lines in culture. *Acta Pathol Microbiol Scand A Pathol* 89:393–402
1264. Haugen Å, Laerum OD, Bock E (1981) Responsiveness of fetal rat brain cells to glia maturation factor during neoplastic transformation in cell culture. *Acta Pathol Microbiol Scand A Pathol* 89:393–402
1265. Hauser SL, Bhan AK, Gilles FM, Hoban CJ, Reinherz EL, Schlossmann SF, Weiner HL (1983) Immunohistochemical staining of human brain with monoclonal antibodies that identify lymphocytes, monocytes and the Ia antigen. *J Neuroimmunol* 5:197–205
1266. Hauw JJ, Berger B, Escourolle R (1975) Electron microscopic study of developing capillaries of human brain. *Acta Neuropathol (Berl)* 31:229–242
1267. Hawkes R, Niday E, Matus A (1982) Monoclonal antibodies identify novel neural antigens. *Proc Natl Acad Sci (USA)* 79:2410–2414
1268. Hayakawa T, Takakura K, Abe H, Yoshimoto T, Tanaka R, Sugita K, Kikuchi H, Uozumi T, Hori T, Fukui H, Ushio Y, Nomura K, Matsutani M, Mohri N, Kumanishi T, Aozasa K, Nagashima K (1994) Primary central nervous system lymphoma in Japan. A retrospective co-operative study by CNS-Lymphoma Study Group in Japan. *J Neuro Oncol* 19:197–215
1269. Hayashi K, Hoshida Y, Horic Y, Takahashi K, Taguchi K, Sanobe H, Ohtsuki Y, Akagi T (1991) Immunohistochemical study on the distribution of a and b sub-units of S-100 protein in brain tumors. *Acta Neuropathol (Berl)* 81:657–663
1270. Hayashi T, Ohara N, Jeon HJ, Akagi S, Takahashi K, Akagi T, Nomba S (1993) Gliosarcoma with features of chondroblastic osteosarcoma. *Cancer* 72:850–855
1271. Hayashi Y, Yamashita Y, Yamaguchi K (1991) Timing and role of p53 gene mutations in the recurrence of glioma. *Biochem Biophys Res Commun* 180:1145–1150
1272. Hayes RL, Koslow M, Hiesiger EM, Hymes KB, Hochster HS, Moore EJ, Pierz DM, Chen DK, Buzilovich GN, Ransohoff J (1995) Improved long term survival after intracavitary interleu-

- kin-2 and Lymphokine-activated killer cells for adults with recurrent malignant glioma. *Cancer* 76:5 840–852
1273. Haymaker W, Yenermen MH (1955) Pathological features of colloid cysts of the third ventricle. A consideration of 60 cases. *Neurology* 8:788
  1274. Haymaker W, Rubinstein LJ, Miquel J (1972) Brain tumours in irradiated monkeys. *Acta Neuropathol (Berl)* 20:267–277
  1275. Hayman LA, Evans RA, Ferrell RE, Faler LM, Ostrow P, Riccardi VM (1982) Familial cavernous angiomas: natural history and genetic study over a 5-year period. *Am J Med Genet* 11:147–152
  1276. Hazen S, Freidberg SR, Thomas C, Wallman J, Clerkin EP, Lo TCM (1989) Multiple distinct intracranial tumors: association of pinealoma and craniopharyngioma. *Surg Neurol* 31:381–386.
  1277. Hazuka MB, DeBiose DA, Henderson RH, Kinzie JJ (1992) Survival results in adult patients treated for medulloblastoma. *Cancer* 69:2143–2148
  1278. He X, Skapek SX, Wikstrand CJ, Friedman HS, Trojanowski JQ, Kemshead JT, Coakham HB, Bigner SH, Bigner DD (1989) Phenotypic analysis of four human medulloblastoma cell lines and transplantable xenografts. *J Neuropathol Exp Neurol* 48:48–68
  1279. Hedley DW, Friedlander ML, Taylor IW, Rugg CA, Musgrove EA (1983) Method for analysis of cellular DNA content of paraffin-embedded pathological material using flow cytometry. *J Histochem Cytochem* 31:1333–1335
  1280. Hedley DW, Friedlander ML, Taylor IW (1985) Application of DNA flow cytometry to paraffin-embedded archival material of the study of aneuploidy and its clinical significance. *Cytometry* 6:327–333
  1281. Heffelfinger MJ, Dahlin DC, MacCarthy CS, Beabout JW (1973) Chordomas and cartilaginous tumors at the skull base. *Cancer* 32:410–420
  1282. Hegarty TJ, Thornton AF, Diaz RF, Chandler WF, Ensminger WD, Junck L, Page AM, Gebarski SS, Hood TW, Stetson PL, Tankanow RM, McKeever PE, Lichter AS, Greenberg HS (1990) Intra-arterial bromodeoxyuridine radiosensitization of malignant gliomas. *Int J Radiat Oncol Biol Phys* 19:421–428
  1283. Hegedus B (1962) Recherches histochimiques sur la surcharge graisseuse du neurinome. Proceedings of the IVth International Congress on Neuropathology, Munich, vol 1. Thieme, Stuttgart, pp 58–60
  1284. Heidelberger KP, LeGolvan DP (1974) Wiskott-Aldrich syndrome and cerebral neoplasia: report of a case with localized reticulum cell sarcoma. *Cancer* 33:280–284
  1285. Heisiger EM, Voorlies RM, Basler GA, Lipshutz LE, Posner JB, Shapiro WR (1986) Opening the blood-tumor barriers in experimental brain tumors: the effect of intracarotid hyperosmolar mannitol on capillary permeability and blood flow. *Ann Neurol* 19:50–59
  1286. Helle TL, Britt RH, Colby TV (1984) Primary lymphoma of the central nervous system. Clinicopathological study of experience at Stanford. *J Neurosurg* 60:94–103
  1287. Helpap B (1978) Extraadrenale Paraganglien und Paragangliome. Stuttgart, Thieme
  1288. Helseth A, Mørk S (1989) Neoplasms of the central nervous system in Norway. III Epidemiological characteristics of intracranial gliomas according to histology. *APMIS* 97:547–555
  1289. Helseth A, Langmark F, Mørk S (1988) Neoplasms of the central nervous system in Norway. II. Descriptive epidemiology of intracranial neoplasms 1955–1984. *APMIS* 96:1066–1074
  1290. Hemmati-Brivanlou A, Kelly OG, Melton DA (1994) Follistatin an antagonist of activin, is expressed in the Spemann organizer and displays direct neuralizing activity. *Cell* 77:283–295
  1291. Henderson SD, Kimler BF, Morants RA (1981) Radiation therapy of 9L rat brain tumors. *Int J Radiat Oncol Biol Phys* 7:497–502
  1292. Henderson SD, Kimler BF, Scanlan MF (1982) Interaction of hyperthermia and radiation on the survival of synchronous 9L cells. *Radiat Res* 92:146–159
  1293. Hennessy TG, Stern WE, Herrick SE (1967) Cerebellar hemangioblastoma: erythropoietic activity by radioiron assay. *J Nucl Med* 8:601–606
  1294. Henry JM, Heffner RR, Dillard SH, Earle KM, Davies RL (1974) Primary malignant lymphomas of the central nervous system. *Cancer* 34:1293–1302
  1295. Henschen F (1910) Über Geschwülste der hinteren Schädelgrube, insbesondere des Kleinhirnbrückenwinkels. Fischer, Jena
  1296. Henschen F (1915) Zur Histologie und Pathogenese der Kleinhirnbrückenwinkeltumoren. *Arch Psych* 56:1–22

1297. Henschen F (1955) Tumoren des Zentralnervensystems und seiner Hüllen. Handbuch spez pathol Anat u Histol, vol 13/3, Springer, Berlin Göttingen Heidelberg
1298. Henson JW, Schnitker BL, Correa KM, von Deimling A, Fassbender F, Xu H-J, Benedict WF, Yandell DW, Louis DN (1994) The retinoblastoma susceptibility (Rb) gene is involved in the malignant progression of human astrocytomas. *Ann Neurol* 36:714–721
1299. Henson RA, Urich H (1982) Cancer and the nervous system. The neurological manifestations of systemic malignant disease. Blackwell, Oxford
1300. Herbert J, Cavallaro T, Dwork AJ (1990) A marker for primary choroid plexus neoplasms. *Am J Pathol* 136:1317–1325.
1301. Herbst KD, Cordes MP, Justice GR (1976) Successful therapy with methotrexate of a multicentric mixed lymphoma of the central nervous system. *Cancer* 38:1476–1478
1302. Herman JG, Latif F, Weng Y, Lerman MI, Zbar B, Liu S, Samid D, Duan DS, Gnarr JR, Linehan WM (1994) Silencing of the VHL tumor suppressor gene by DNA methylation in renal carcinoma. *Proc Natl Acad Sci USA* 91:9700–9704
1303. Herman MM, Rubinstein LJ (1984) Divergent glial and neuronal differentiation in a cerebellar medulloblastoma in an organ culture system: in vitro occurrence of synaptic ribbons. *Acta Neuropathol (Berl)* 65:10–24
1304. Hermanson M, Nistér M, Betsholtz C, Heldin C-H, Westermark B, Funa K (1988) Endothelial cell hyperplasia in human glioblastoma: coexpression of mRNA for platelet-derived growth factor (PDGF) B chain and PDGF receptor suggests autocrine growth stimulation. *Proc Natl Acad Sci USA* 85:7748–7752
1305. Hermanson M, Funa K, Hartman M, Claesson-Welsh L, Heldin C-H, Westermark B, Nister M (1992) Platelet-derived growth factor and its receptors in human glioma tissue: expression of messenger RNA and protein suggests the presence of autocrine and paracrine loops. *Cancer Res* 52:3213–3219
1306. Herndon RM, Rubinstein LJ, Freeman JM, Mathieson G (1970) Light and electron microscopic observations on Rosenthal fibers in Alexander's disease and in multiple sclerosis. *J Neuropathol Exp Neurol* 29:524–551
1307. Herpers MJHM, Budka H (1984) Glial fibrillary acidic protein (GFAP) in oligodendroglial tumors: gliofibrillary oligodendroglioma and transitional oligoastrocytoma as subtypes of oligodendroglioma. *Acta Neuropathol (Berl)* 64:265–272
1308. Herpers MJHM, Budka H (1985) Primitive neuroectodermal tumors including the medulloblastoma: glial differentiation signaled by immunoreactivity for GFAP is restricted to the pure desmoplastic medulloblastoma ("arachnoidal sarcoma of the cerebellum"). *Clin Neuropathol* 4:12–18
1309. Herpers MJHM, Ramaekers FCS, Aldeweireldt J, Moesker O, Scooff J (1986) Co-expression of glial fibrillary acidic protein and vimentin-type intermediate filaments in human astrocytomas. *Acta Neuropathol (Berl)* 70:333–339
1310. Herregodts P, Vloeberghs M, Schmedding E, Goossens A, Stadnik T, D'Haens J (1991) Solitary dorsal intramedullary schwannoma. Case report. *J Neurosurg* 74:816–820
1311. Herrick MK, Rubinstein LJ (1979) The cytological differentiating potential of pineal parenchymal neoplasms (true pinealomas): a clinicopathologic study of 28 tumours. *Brain* 102:289–320
1312. Herrschaft H (1968) Die Teratoma des Zentralnervensystems. *Dtsch Ztschr Nervenheilkd* 194:344–365
1313. Herter T, Brandt M, Szüwart U (1988) Cavernous hemangiomas in children. *Childs Nerv Syst* 4:123–127
1314. Hertz DA, Shapiro K, Shulman K (1980) Intracranial meningioma of infancy, childhood and adolescence: review of the literature and addition of 9 case reports. *Childs Brain* 7:43–56
1315. Hessler RB, Lopes MBS, Frankfurter A, Reidy J, VandenBerg SR (1992) Cytoskeletal immunohistochemistry of central neurocytomas. *Am J Surg Pathol* 16:1031–1038
1316. Heuch I, Blom GP (1986) Glioblastoma multiforme in three family members including one case of true multicentricity. *J Neurol* 233:142–144
1317. Hickey WF, Lee V, Trojanowski JQ, McMillan LJ, McKearn TJ, Gonatas NK (1983) Immunohistochemical application of monoclonal antibodies against myelin basic protein and neurofilament triplet protein subunits: advantage over antisera and technical limitations. *J Histochem Cytochem* 31:1126–1135

1318. Higazi I (1963) Tuberculoma of the brain. A clinical and angiographic study. *J Neurosurg* 20:378–386
1319. Hildebrand J, Sahmoud T, Mignolet F, Grucher JM, Afra D, The EORTC Brain Tumor Group (1994) Adjuvant therapy with dibromodulcitol and BCNU increases survival of adults with malignant gliomas. *Neurology* 44:1479–1483
1320. Hildebrandt K (1906) Zur Kenntnis der gliomatösen Neubildungen des Gehirns mit besonderer Berücksichtigung der ependimären Gliome. *Virchows Arch* 185:341–359
1321. Hince TA, Roscoe JP (1978) Fibrinolytic activity of cultured cells derived during ethylnitrosourea induced carcinogenesis of rat brain. *Br J Cancer* 37:424–433
1322. Hinton D, Halliday WC (1984) Primary rhabdomyosarcoma of the cerebellum. A light electron microscopic and immunohistochemical study. *J Neuropathol Exp Neurol* 43:439–449
1323. Hinton D, Mobbs EG, Sima AA, Hanna W (1983) Steroid receptors in meningiomas. A histochemical and biochemical study. *Acta Neuropathol (Berl)* 62:134–140
1324. Hirakawa K, Suzuki K, Neda S, Handa J (1986) Fetal origin of the medulloblastoma: evidence from growth analysis of two cases. *Acta Neuropathol (Berl)* 70:227–234
1325. Hirano A (1978) Some contributions of electron microscopy to the diagnosis of brain tumors. *Acta Neuropathol (Berl)* 43:119–128
1326. Hirano A, Ghatak NR (1974) The fine structure of colloid cysts of the third ventricle. *J Neuropathol Exp Neurol* 33:333–341
1327. Hirano A, Ghatak NR, Wilsoff HS, Zimmerman HM (1971) An epithelial cyst of the spinal cord. An electron microscopic study. *Acta Neuropathol (Berl)* 18:214–223
1328. Hirano A, Ghatak NR, Zimmerman HM (1973) Fenestrated blood vessels in craniopharyngioma. *Acta Neuropathol (Berl)* 26:171–177
1329. Hirano A, Llena JF, Chung HD (1975) Some new observations in an intracranial germinoma. *Acta Neuropathol (Berl)* 32:103–113
1330. Hirano A, Matsui T. (1975) Vascular structures in brain tumors. *Hum Pathol* 6:611–621
1331. Hirano A, Shin W-Y (1979) Unattached presynaptic terminals in a cerebellar neuroblastoma in the human. *Neuropathol Appl Neurobiol* 5:63–70
1332. Hirano A, Zimmerman HM, Levine S (1964) The fine structure of cerebral fluid accumulation. III. Extracellular spread of cryptococcal polysaccharides in the acute stage. *Am J Pathol* 45:1–19
1333. Hirn M, Ghandour MS, Deagostini-Bazin H, Goridis C (1983) Molecular heterogeneity and structural evolution during cerebellar ontogeny detected by monoclonal antibody of the mouse cell surface antigen BSP-2. *Brain Res* 265:87–100
1334. Hirokawa K, Suzuki K, Veda S, Nakagawa Y, Yoshino E, Ibayashi N, Hayashi K (1984) Multivariate analysis of factors affecting postoperative survival in malignant astrocytoma. *J Neurooncol* 2:331–340
1335. Hirose T, Sano T, Hizawa K (1986) Ultrastructural localization of S-100 protein in neurofibroma. *Acta Neuropathol (Berl)* 69:103–110
1336. Hirose T, Scheithauer BW, Lopes MBS, VandenBerg SR (1994) Dysembryoplastic neuroepithelial tumor (DNT): an immunohistochemical and ultrastructural study. *J Neuropathol Exp Neurol* 53:184–195
1337. Hirose T, Scheithauer BW, Lopes MBS, Gerber HA, Altermatt HJ, Harner SG, VandenBerg SR (1995) Olfactory neuroblastoma. An immunohistochemical, ultrastructural, and flow cytometric study. *Cancer* 76:4–19
1338. Hirschberg H (1984) Endothelial growth factor production in cultures of human glioma cells. *Neuropath Appl Neurobiol* 10:33–42
1339. His W (1889) Die Neuroblasten und deren Entstehung im embryonalen Mark. *Abhandl Math Phys Kl Königl Sächs Ges Wiss* 26:313–372
1340. Hitchcock ER, Morris CS (1988) Mononuclear cell infiltration in central portions of human astrocytomas. *J Neurosurg* 68:432–437
1341. Hitotsumatsu T, Iwaki T, Fukui M (1994) Cytoplasmic inclusions of astrocytic elements of glial tumors: special reference to round granulated body and eosinophilic hyaline droplets. *Acta Neuropathol (Berl)* 88:501–510
1342. Hitselberger WE, Kernohan JW, Uihlein A (1961) Giant cell fibrosarcoma of the brain. *Cancer* 14:841–852

1343. Ho DM, Wong TT, Lin HC (1991) Choroid plexus tumors in childhood. Histopathologic study and clinico-pathological correlation. *Childs Nerv Syst* 7:437-441
1344. Ho KL (1981) Schwannoma of the trochlear nerve. *J Neurosurg* 55:132-135
1345. Ho KL (1983) Concurrence of subependymoma and heterotopic leptomeningeal neuroglial tissue. *Arch Pathol Lab Med* 107:136-142
1346. Ho KL (1984) Ultrastructure of cerebellar capillary hemangioblastoma. I Weibel-Palade bodies and stromal cell histogenesis. *J Neuropathol Exp Neurol* 43:592-608
1347. Ho KL (1985) Ectodermosis phusalphora and chordoma: a comparative ultrastructural study. *Clin Neuropathol* 4:77-86
1348. Ho KL (1985) Ultrastructure of cerebellar capillary hemangioblastoma. IV Pericytes and their relationship to endothelial cells. *Acta Neuropathol (Berl)* 67:254-264
1349. Ho KL (1986) Ultrastructure of cerebellar capillary hemangioblastoma. V Large pinocytotic vacuolar bodies (megapinocytotic vesicles) in endothelial cells. *Acta Neuropathol (Berl)* 70:117-126
1350. Ho KL (1987) Ultrastructure of cerebellar capillary hemangioblastoma. VI Concentric lamellar bodies of endoplasmic reticulum in stromal cells. *Acta Neuropathol (Berl)* 74:345-353
1351. Ho KL (1990) Septate-like junction in myxopapillary ependymoma. *Acta Neuropathol (Berl)* 479:430-437
1352. Hoag G, Sima AAF, Rozdilsky B (1986) Astroblastoma revisited: a report of three cases. *Acta Neuropathol (Berl)* 70:10-16
1353. Hoang-Xuan K, Merel P, Veger F, Hugot J-P, Cornu P, Delattre J-Y, Poisson M, Thomas G, Delattre O (1995) Analysis of the NF2 tumor-suppressor gene and of chromosome 22 deletions in gliomas. *Int J Cancer* 60:478-481
1354. Hoch-Ligeti C (1957) Effects of prolonged administration of spermicidal contraceptives on rats kept on low-protein or full diet. *J Nat Cancer Inst USA* 18:661-685
1355. Hoch-Ligeti C, Russell DS (1950) Primary tumours of the brain and meninges in rats fed with 2-acetylaminofluorene. *UICC* 7:126-129
1356. Hochberg F, Toniolo P, Cole P (1984) Head trauma and seizures as risk factors of glioblastoma. *Neurology* 34:1511-1514
1357. Hochberg F, Toniolo P, Cole P (1990) Non occupational risk indicators of glioblastoma in adults. *J Neurooncol* 8:55-60
1358. Hochberg FH, Miller DC (1988) Primary central nervous system lymphoma. *J Neurosurg* 68:835-853
1359. Hochberg FH, Pruitt A (1980) Assumptions in the radiotherapy of glioblastoma. *Neurology* 30:907-911
1360. Hochberg RH, Miller G, Schooley RT, Hirsch MS, Faorino P, Henle W (1983) Central nervous system lymphoma related to Epstein-Barr virus. *N Engl J Med* 309:745-748
1361. Hoessly GF, Olivecrona H (1955) Report on 280 cases of verified parasagittal meningioma. *J Neurosurg* 12:614-626
1362. Hoff DJ, Tamperi D, Just N (1993) Imaging of spinal cord hemangioblastomas. *Can Assoc Radiol J* 44:377-383
1363. Hoffman H, Solonink DS, Humphreys RP, Drake JM, Becker LE, De Lima O, Piatt JH (1993) Management and outcome of low-grade astrocytoma of the midline in children: a retrospective review. *Neurosurgery* 33:964-971
1364. Hoffman HJ (1987) Benign brain stem gliomas in children. *Prog Exp Tumor Res* 30:154-159
1365. Hoffman HJ, Duffner PK (1985) Extraneural metastases of central nervous system tumors. *Cancer* 56:1778-1782
1366. Hoffman HJ, Hendrick EB, Humphreys RP, Bunac JR, Armstrong DL, Jenkin RDT (1977) Management of craniopharyngioma in children. *J Neurosurg* 47:218-227
1367. Hoffman HJ, Yoshida M, Becker LE, Hendrick EB, Humphreys RP (1983) Pineal region tumors in childhood. Experience at The Hospital for Sick Children. *Concepts in Pediatric Neurosurgery* 4:360-386
1368. Hoffman HJ, De Silva M, Humphreys RP, Drake JM, Smith ML, Blaser SI (1992) Aggressive surgical management of craniopharyngiomas in children. *J Neurosurg* 76:47-52
1369. Hoffman SF, Rorke LB (1971) On finding striated muscle in the brain. *J Neurol Neurosurg Psychiatry* 34:761-764



1370. Hoffmeyer S, Assum G, Kaufmann D, Krone W (1994) Unequal expression of NF1 alleles (Letter). *Nat Genet* 94:331
1371. Hohwieler ML, Theodore PAC, Silverman ML, Freidberg SR (1986) Brain necrosis after radiotherapy for primary intracerebral tumor. *Neurosurgery* 18:67–74
1372. Holbach KH (1975) Zur Herkunft intrasellärer raumfordernder Zysten. *Zbl Neurochir* 36:19–26
1373. Holbach KH, Gullotta F (1977) Zur Formalgenese intrasellärer und intraventrikulärer Zysten. *Neurochirurgia* 20:186–188
1374. Holden J, Dolman CL, Churg A (1987) Immunohistochemistry of meningioma including the angioblastic type. *J Neuropathol Exp Neurol* 46:50–56
1375. Holimon JL, Rosenblum WI (1971) “Gangliorhabdomyosarcoma”: a tumor of ectomesenchyme. Case report. *J Neurosurg* 34:417–422
1376. Hollstein M, Sidransky D, Vogelstein B, Harris CC (1991) p53 mutations in human cancers. *Science* 253:49–53
1377. Holzner H (1954) Ungewöhnliche Metastasierung eines Chordoms. *Zentralbl Allg Pathol* 92:12–18
1378. Hoover R, Fraumeni JF (1973) Risk of cancer in renal transplant recipients. *Lancet* 2:55–57
1379. Hopewell JW (1979) Late radiation damage to the central nervous system: a radiobiological interpretation. *Neuropathol Appl Neurobiol* 5:329–343
1380. Hopewell JW (1983) Radiation effects on vascular tissue. In: Potten CS, Hendry JH (eds) *Cytotoxic insult to tissue*. Churchill Livingstone, Edinburgh, pp 228–257
1381. Hopewell JW, Wright EA (1970) The nature of latent cerebral irradiation damage and its modification by hypertension. *Br J Radiol* 43:161–167
1382. Hopewell JW, Wright EA (1969) The importance of implantation site in cerebral carcinogenesis in rats. *Cancer Res* 29:1927–1931
1383. Hoppe-Hirsch E, Renier D, Lellouch-Tupiana A, Sainte-rose C, Pierre-Kahn A, Hirsch JF (1990) Medulloblastoma in childhood: progressive intellectual deterioration. *Childs Nerv Syst* 6:60–65
1384. Hori A, Ikeda K (1982) Symmetric ganglionic hamartoma of hypothalamus appearing as four “mamillary” bodies. *Acta Neuropathol (Berl)* 56:238–240
1385. Hori A, Altmannsberger M, Spoerri O, Beuche W (1985) Granular cell tumor in the third ventricle: case report with histological, electron-microscopic, immunohistochemical and necropsy findings. *Acta Neurochir (Wien)* 74: 49–52
1386. Hori A, Weiss R, Schaake T (1988) Ganglioglioma containing osseous tissue and neurofibrillary tangles. *Arch Pathol Lab Med* 112:653–655
1387. Hornef M, Wagner H, Fricke L, Bein G, Kirchner H (1995) Immunocytochemical detection of Epstein-Barr virus antigens in peripheral B lymphocytes after renal transplantation. *Transplantation* 59:138–140
1388. Horoupian DS, Kerson LA, Saiontz H, Valsamis M (1974) Paraganglioma of the cauda equina. Clinicopathologic and ultrastructural studies of an unusual case. *Cancer* 33:1337–1348
1389. Horowitz MB, Hall WA (1991) Central nervous System germinomas. A review. *Arch Neurol* 48:652–657
1390. Horrax G, Wu WQ (1951) Postoperative survival of patients with intracranial oligodendroglioma with special reference to radical removal. A study of 26 patients. *J Neurosurg* 8:473–479
1391. Horst H-A, Scheithauer BW, Kelly PJ, Kovach JS (1992) Distribution of transforming growth factor-beta<sub>1</sub> in human astrocytomas. *Hum Pathol* 23:1284–1288
1392. Horstmann E (1954) Die Faserlgia des Selachiergehirns. *Z Zellforsch* 39:588–617
1393. Horteaga Del Rio P (1932) Estructura y sistematizacion de los gliomas y paragliomas. *Arch Espan Oncol* 2:441–678
1394. Horteaga Del Rio P (1945) Nomenclatura y clasificacion de los tumores del Sistema Nervioso. Lopez and Etchegoyen, Buenos Aires
1395. Horten BC, Rubinstein LJ (1976) Primary cerebral neuroblastoma: a clinicopathologic study of 35 cases. *Brain* 99:735–756
1396. Horten BC, Ulrich H, Rubinstein LJ, Montague SR (1977) The angioblastic meningioma: a reappraisal of a nosological problem. *J Neurol Sci* 31:387–410

1397. Horten BC, Urich H, Stefoski D (1979) Meningiomas with conspicuous plasma cell-lymphocytic components: a report of five cases. *Cancer* 43:258–264
1398. Horton WA, Wong V, Eldridge R (1976) Von Hippel-Lindau disease. Clinical pathological manifestation in nine families with 50 affected members. *Arch Int Med* 136:769–777
1399. Horwich A, Riccardi VN, Francke U (1983) Aqueductal stenosis leading to hydrocephalus – an unusual manifestation of neurofibromatosis. *Am J Med Genetics* 14:577–583
1400. Hoshino T (1981) Cellular aspects of human brain tumors (gliomas). *Neurobiol* 2:167–204
1401. Hoshino T (1984) Heterogeneity of tumor cell DNA content. *Progr Exp tumor Res* 27:83–91
1402. Hoshino T (1984) A commentary on the biology and growth kinetics of low-grade and high-grade gliomas. *J Neurosurg* 61:895–900
1403. Hoshino T (1991) Cell kinetics of brain tumors. In: Salzman M (ed) *Neurobiology of brain Tumors*, vol 4. Williams and Wilkins, Baltimore, pp 145–159
1404. Hoshino T, Wilson CB (1979) Cell kinetic analyses of human malignant brain tumors (gliomas). *Cancer* 44:956–962
1405. Hoshino T, Wilson CB, Rosenblum ML, Barker M (1975) Chemotherapeutic implications of growth fraction and cell cycle time in glioblastomas. *J Neurosurg* 43:127–135
1406. Hoshino T, Nomura K, Wilson CB, Knebel DB, Gray JW (1978) The distribution of nuclear DNA from human brain-tumor cells: flow cytometric studies. *J Neurosurg* 49:13–21
1407. Hoshino T, Townsend JJ, Muraoka I, Wilson CB (1980) An autoradiographic study of human gliomas: growth kinetics of anaplastic astrocytoma and glioblastoma multiforme. *Brain* 103:967–984
1408. Hoshino T, Knebel KD, Rosenblum ML, Dougherty DV, Wilson CB (1982) Clonogenicity of multiple populations of human glioma cells in vitro sorted by DNA content. *Cancer* 50:997–1002
1409. Hoshino T, Nagashima T, Murovic JA, Levin EM, Levin VA, Rupp SM (1985) Cell kinetic studies of in situ brain tumors with bromodeoxyuridine. *Cytometry* 6:627–632
1410. Hoshino T, Nagashima T, Cho KG, Murovic JA, Hodes JE, Wilson CB, Edwards MSB, Pitts LH (1986) S-phase fraction of human brain tumors in situ measured by uptake of bromodeoxyuridine. *Int J Cancer* 38:369–374
1411. Hoshino T, Nagashima T, Murovic JA, Wilson CB, Davis RL (1986) Proliferative potential of human meningiomas of the brain. A cell kinetics study with bromodeoxyuridine. *Cancer* 58:1466–1472
1412. Hoshino T, Rodriguez LA, Cho KG, Lee KS, Wilson CB, Edwards MSB, Levin VA, Davis RL (1988) Prognostic implications of the proliferative potential of low-grade astrocytomas. *J Neurosurg* 69:839–842
1413. Hoshino T, Prados M, Wilson CB, Cho KG, Lee KS, Davis R (1989) Prognostic implications of the bromodeoxyuridine labeling index of human gliomas. *J Neurosurg* 71:335–341
1414. Hossmann KA, Wechsler W (1965) Zur Feinstruktur menschlicher Spongioblastome. *Dtsch Ztschr Nervenheilk* 187:327–351
1415. Hossmann KA, Blöink M, Wilmes F, Wechsler W (1980) Experimental peritumoral edema of the cat brain. *Adv Neurol* 28: 323–340
1416. Hossmann KA, Mies G, Paschen W, Szabo L, Dolan E, Wechsler W (1986) Regional metabolism in experimental brain tumors. *Acta Neuropathol (Berl)* 69:139–147
1417. Houthoff HJ, Poppema S, Ebels EJ, Elema JD (1978) Intracranial malignant lymphomas. A morphologic and immunocytologic study of twenty cases. *Acta Neuropathol (Berl)* 44:203–210
1418. Howe GR, Burch JD, Chiarelli AM, Risch HA, Choi BCK (1989) An exploratory case-control study of brain tumors in children. *Cancer Res* 49:4349–4352
1419. Hoye SJ, Hoarr CS Jr, Murray JI (1960) Extracranial meningioma presented as tumor of the neck. *Am J Surg* 100:486–389
1420. Hoyt JW, Gown AM, Kim DK, Berger MS (1995) Analysis of proliferative grade in glial neoplasms using antibodies to the Ki-67 defined antigen and PCNA in formalin fixed, deparaffinized tissues. *J Neurooncol* 24:163–169
1421. Hoyt WF, Meshel LG, Lessell S, Schatz NJ, Suckling RD (1973) Malignant optic nerve glioma of adulthood. *Brain* 96:121–132
1422. Hoytema GJ, Winckel WEF (1957) Zur Frage des primären Plexuskarzinoms. *Zbl Neurochir* 17:353–363

1423. Hsu DW, Pardo FS, Efird JT, Linggood RM, Hedley-White T (1994) Prognostic significance of proliferative indices in meningiomas. *J Neuropathol Exp Neurol* 53:247-255
1424. Huang CI, Chion WH, Ho DM (1987) Oligodendroglioma occurring after radiation therapy for pituitary adenoma. *J Neurol Neurosurg Psychiatry* 50:1619-1624
1425. Huang H-JS, Yee J-K, Shew J-Y, Chen P-L, Bookstein R, Freimann T, Lee EY-HP, Lee W-H (1988) Suppression of the neoplastic phenotype by replacement of the retinoblastoma gene product in human cancer cell. *Science* 242:1563-1566
1426. Huang SK, Nobiling R, Schachner M, Taugner R (1984) Interstitial and parenchymal cells in the pineal gland of the golden hamster. A combined thin-section, freeze-fracture and immunofluorescence study. *Cell Tissue Res* 235:327-337
1427. Hubbard BM, Hopewell JW (1979) Changes in the neuroglial cell population of the rat spinal cord after local x-irradiation. *Br J Radiol* 52:816-821
1428. Hubbard BM, Hopewell JW (1980) Quantitative changes in the cellularity of the rat subependymal plate after x-irradiation. *Cell and Tissue kinetics* 13:403-413
1429. Huh K (1964) A study of the incidence of calcification in a histological survey of surgical biopsies of meningiomas. *J Neurosurg* 21:751-757
1430. Huisman TWA, Tanghe HLJ, Koper JW, Reubi JC, Foekens JA, Avezaat CJJ, Braakman R, Lamberts SWJ (1991) Progesterone, oestradiol, somatostatin and epidermal growth factor receptors on human meningiomas and their CT characteristics. *Eur J Cancer*, 27:1453-1457
1431. Humphrey PA, Wong AJ, Vogelstein B, Friedman HS, Werner MH, Bigner DD, Bigner SH (1988) Amplification and expression of the epidermal growth factor receptor in human glioma xenografts. *Cancer Res* 48:2231-2238
1432. Hunt P, Gulisano M, Cook M, Sham M-H, Faiella A, Wilkinson D, Boncinelli E, Krumlauf R (1991) A distinct Hox code for the branchial region of the vertebrate head. *Nature* 353:861-864
1433. Hunt SJ, Johnson PC (1989) Melanotic ganglioglioma of the pineal region. *Acta Neuropathol (Berl)* 79:222-225
1434. Hunter SB, Bandea C, Swan D, Abbott K, Varma VA (1993) Mutations in the p53 gene in human astrocytomas: detection by single-strand conformation polymorphism analysis and direct DNA sequences. *Mod Pathol* 6:442-445
1435. Hunter T (1984) The epidermal growth factor receptor gene and its product. *Nature* 311:414-416
1436. Hunter T (1991) Cooperation between oncogenes. *Cell* 64:249-270
1437. Hurt MR, Moossy J, Donovan-Peluso M, Locker J (1992) Amplification of epidermal growth factor receptor gene in gliomas: histopathology and prognosis. *J Neuropathol Exp Neurol* 51:84-90
1438. Hurt MR, Moossy J, Donovan PM, Locker J (1992) Amplification of epidermal growth factor receptor gene in gliomas: histopathology and prognosis. *J Neuropathol Exp Neurol* 51:84-90
1439. Husain AN, Leestma JE (1986) Cerebral astroblastoma: immunohistochemical and ultrastructural features. *J Neurosurg* 64:657-611
1440. Husain MM, Garcia JH (1976) Cerebral radiation necrosis: vascular and glial features. *Acta Neuropathol (Berl)* 36:381-385
1441. Huson SM (1987) The different forms of neurofibromatosis. *Br Med J* 294:1113-1114
1442. Huson SM (1994) Neurofibromatosis 1: a clinical and genetic overview. In: Huson SM, Hughes RAC (eds) *The neurofibromatoses*. Chapman and Hall, London, pp 160-204
1443. Huson SM, Harper PS, Hourihan MD, Cole G, Weeks RD, Compston DAS (1986) Cerebellar hemangioblastoma and von Hippel-Lindau disease. *Brain* 109:1297-1310
1444. Hussein AM, Savaraj N, Feun LG, Ganjei P, Donnelly E (1989) Carcinomatous meningitis from transitional cell carcinoma of the bladder: case report. *J Neurooncol* 7:255-260
1445. Hydén H, McEwen B (1986) A glial protein specific for the nervous system. *Proc Natl Acad Sci USA* 55:354-358
1446. Ibrahim AWM, Farag H, Naguib M, Ibrahim E (1986) Neuroepithelial (colloid) cyst of the third ventricle in identical twins. *J Neurosurg* 65:401-403
1447. Ibrahim MZM, Adams CWM (1965) The relation between enzyme activity and neuroglia in early plaques of multiple sclerosis. *J Pathol Bacteriol* 90:239-243
1448. Iglesias-Rozas JR, Collia-Fernandez F (1980) Primeros estadios de los tumores del sistema nervioso en el hombre. *Morf Norm Patol* 4:511-525

1449. Iglesias-Rozas JR, Kroh H, Sauer E, Sariogler N (1989) Disseminated melanomatosis of the central nervous system and other organs: a case report. *Clin Neuropathol* 8:11–15
1450. Ikeda T, Matsuo T, Kohnos S, Tashiro T, Maeda H (1983) Early stage of development of transplacentally induced gliomas with ethylnitrosourea in rats. *Acta Pathol Jpn* 33:237–247
1451. Ikeda T, Mashimoto H, Iwasaki K, Shimokawa I, Matsuo T (1989) A sequential ultrastructural and histo-autoradiographic study of early neoplastic lesions in ethylnitrosourea induced rat glioma. *Acta Pathol Jpn* 39:487–495
1452. Ilgren EB, Stiller CA (1986) Cerebellar astrocytomas: therapeutic management. *Acta Neurochir (Wien)* 81:11–26
1453. Ilgren EB, Stiller CA (1987) Cerebellar astrocytomas. I. macroscopic and microscopic features. *Clin Neuropathol* 6:185–200
1454. Ilgren EB, Stiller CA (1987) Cerebellar astrocytomas II. pathological features indicative of malignancy. *Clin Neuropathol* 6:201–214
1455. Ilgren EB, Teddy PJ (1984) Chemodectoma of the cauda equina: case report. *Clin Neuropathol* 3:148–152
1456. Ilgren EB, Stiller CA, Hughes JT, Silberman D, Steckel N, Kaye A (1984) Ependymomas: A clinical and pathologic study. II. Survival features. *Clin Neuropathol* 3:122–127
1457. Ilgren EB, Kinnier-Wilson LM, Stiller CA (1985) Gliomas in neurofibromatosis: a series of 89 cases with evidence of enhanced malignancy in associated cerebellar astrocytomas. In: Sommers SC, Rosen PP, Fechner RE (eds) *Pathol Ann* 20:331–358
1458. Imamoto K, Paterson JA, Leblond CP (1978) Radioautographic investigation of gliogenesis in the corpus callosum of young rats. I. Sequential changes in oligodendrocytes. *J Comp Neurol* 180:115–138
1459. Imes RK, Hoyt WF (1986) Childhood chiasmal gliomas: update on the fate of patient in the 1969 San Francisco study. *Br J Ophthalmol* 70:179–182
1460. Imperato JP, Paleologos NA, Vick NA (1990) Effects of treatment on long-term survivors with malignant astrocytomas. *Ann Neurol* 28:818–822
1461. Imura H, Kato Y, Nakai Y (1987) Endocrine aspects of tumors arising from suprasellar, third ventricular regions. *Progr Exp Tumor Res* 30:313–324
1462. Inagawa T, Kamiya K, Hosoda I, Yano T (1989) Jugular foramen meningioma. *Surg Neurol* 31:295–299
1463. Ingraham FD, Bailey OT (1946) Cystic teratomas and teratoid tumours of the central nervous system in infancy and childhood. *J Neurosurg* 3:511–532
1464. Innes JRM, Carsten A (1961) Demyelination or malacic myelopathy. *Arch Neurol (Chic)* 4:190–199
1465. Inoue HK, Nagamuna H, Ono N (1987) Pathobiology of intracranial germ-cell tumors: immunochemical, immunohistochemical and electron microscopic investigation. *J Neurooncol* 5:105–115
1466. Inoue I, Yoshida J, Kato K (1985) Various immunological parameters studied in patients with malignant brain tumor. Correlation between clinical stage and T cell subsets. *Neurol Med Chir* 25:168–176
1467. Inoue T, Fukui M, Nishio S, Kitamura K, Nagara H (1987) Hyperosmotic blood-brain barrier disruption in brains of rats with an intracerebrally transplanted RG-C6 tumor. *J Neurosurg* 66:256–263
1468. Inoya H, Takakura K, Shitara N, Manaka S (1987) Treatment of medulloblastoma. *Progr Exp Tumor Res* 30:91–99
1469. Ironside JW, Battersby RDE, Dangerfield VJM, Parson MA, Timperly WR, Underwood JCE (1986) Cryostat section assay of oestrogen and progesterone receptors in meningiomas: a clinicopathological study. *J Clin Pathol* 39:44–50
1470. Ironside JW, Battersby RDE, Lawry J, Loomes RS, Day CA, Timperley WR (1987) DNA in the meningioma tissues and explant cell cultures. A flow cytometric study with clinicopathological correlates. *J Neurosurg* 66:588–594
1471. Irving RM, Moffat DA, Hardy DG, Barton DE, Xuereb YH, Maher ER (1994) Somatic NF2 gene mutations in familial and non-familial vestibular schwannoma. *Hum Molec Genet* 3:347–350

1472. Isenberg JS, Mayer P, Butler W, Pfaff-Amesse T, Persing JA (1994) Multiple recurrent Schwannomas of deep and superficial nerves of the upper extremity: a new variant of segmental neurofibromatosis. *Ann Plast Surg* 33:659–663
1473. Ishwar S, Taniguchi RM, Vogel FS (1971) Multiple supratentorial hemangioblastomas: case study and ultrastructural characteristics. *J Neurosurg* 35:396–405
1474. Ito M, Lammertsma AA, Wise RJS, Bernardi S, Frackowiak RSJ, Heather JD, McKenzie CG, Thomas DGT, Jones T (1982) Measurement of regional cerebral blood flow and oxygen utilization in patients with cerebral tumours using  $^{15}\text{O}$  and positron emission tomography: Analytical techniques and preliminary results. *Neuroradiology* 23:63–74
1475. Ito M, Patronas NJ, Di Chiro G, Mansi L, Kennedy C (1986) Effect of moderate level X-radiation to brain on cerebral glucose utilization. *J Comput Assist Tomogr* 10:584–588
- 1475a. Ito S, Hoshino T, Prados MT, Edwards MSB (1992) Cell kinetics of medulloblastomas. *Cancer* 70:671–678
1476. Itoh T, Magnaldi S, White RM, Denklan MB, Hofman K, Naidu S, Bryan N (1995). Neurofibromatosis type I: The evolution of deep gray and white matter MR abnormalities. *Am J Neuroradiol* 15:1513–1519
1477. Itoyama Y, Sternberger NH, Kies MW, Cohen SR, Richardson EP, Webster HF (1980) Immunocytochemical method to identify myelin basic protein in oligodendroglia and myelin sheaths of the human nervous system. *Ann Neurol* 7:157–166
1478. Iwaki T, Fukui M, Takeshita I, Tsuneyoshi M, Tateishi J (1985) Hemangiopericytoma of the meninges: a clinicopathological and immunohistochemical study. *Clin Neuropathol* 7:93–99
1479. Iwaki T, Takeshita I, Fukui M, Kitamura K (1987) Cell kinetics of the malignant evolution of meningothelial meningioma. *Acta Neuropathol (Berl)* 74:243–247
1480. Iyer CGS (1952) Case report of an adamantinoma present at birth. *J Neurosurg* 9:221–228
1481. Jääskeläinen J, Haltia M, Caasonen E, Walström T (1985) The growth rate of intracranial meningiomas and its relation to histology. An analysis of 43 patients. *Surg Neurol* 24:165–172
1482. Jääskeläinen J, Haltia M, Servo A (1986) Atypical and anaplastic meningiomas: radiology, surgery, radiotherapy, and outcome. *Surg Neurol* 25:233–242
1483. Jääskeläinen J, Paetau A, Pyykkö I, Blomstedt G, Palva T, Troupp H (1994) Interface between the facial nerve and large acoustic neurinomas. *J Neurosurg* 80:541–547
1484. Jachimczak P, Bogdahn U, Schneider J, Behl C, Meixensberger J, Apfel R, Dorries R, Schlingsiepen KH, Brysch W (1993) The effect of transforming growth factor-beta2-specific phosphorothioate-anti-sense oligodeoxynucleotides in reversing cellular immunosuppression in malignant glioma. *J Neurosurg* 78:944–951
1485. Jackson P, Thompson RJ (1981) The demonstration of new human brain-specific proteins by high resolution two-dimensional polyacrylamide gel electrophoresis. *J Neurol Sci* 49:429–438
1486. Jacobs DH, McFarlane MJ, Holmes FF (1987) Female patients with meningioma of the sphenoid ridge and additional primary neoplasms of the breast and genital tract. *Cancer* 60:3080–3082
1487. Jacobs JM, Harnsberger HR (1991) Diagnostic angiography and meningiomas. In: Al-Mefty O (ed) *Meningiomas*. Raven, New York, pp 225–241
1488. Jacobs SK, Wilson DJ, Kornblith PL, Grimm EA (1986) Interleukin-2 or autologous lymphokine-activated killer cell treatment of malignant glioma: phase I trial. *Cancer Res* 46:2101–2104
1489. Jacobsen PF, Jenkyn DJ (1987) Four permanent cell lines established from human malignant gliomas: three exhibiting striated muscle differentiation. *J Neuropathol Exp Neurol* 46:431–450
1490. Jacobsen PF, Jenkyn DJ, Papadimitriou JM (1985) Establishment of a human medulloblastoma cell line and its heterotransplantation into nude mice. *J Neuropathol Exp Neurol* 44:472–485
1491. Jacobson M (1978) *Developmental Neurobiology*, 2nd edn. Plenum, New York
1492. Jacobson M (1991) *Developmental neurobiology*, 3rd edn. Plenum, New York
1493. Jaenish R (1988) Transgenic animals. *Science* 240:1468–1474
1494. Jaffe HL (1958) Tumors and tumorous conditions of bones and joints. Lea and Febiger, Philadelphia
1495. Jahn B, Schiebler W, Oimet C, Greengard P (1985) A 38,000 dalton membrane protein (p 38) present in synaptic vesicles. *Proc Natl Acad Sci USA* 82:4137–4141
1496. Jahn E (1940) Die Kraukhaften Befunde an den Hirnkammerwänden im Lichte der Liquor-Hirngewebs-Schrankenfrage. *Beitr Pathol Anat* 104:186–265

1497. James CD, Carlbom E, Dumanski JP, Hansen M, Nordenskjöld M, Collins VP, Cavanee WK (1988) Clonal genomic alterations in glioma malignancy stages. *Cancer Res* 48:5546–5551
1498. James CD, Carlbom E, Nordenskjöld M, Collins VP, Cavanee WK (1989) Mitotic recombination mapping of chromosome 17 in astrocytomas. *Proc Natl Acad Sci USA* 86:2858–2862
1499. James CD, He J, Carlbom E, Mikkelsen T, Ridderheim PA, Cavanee VK, Collins VP (1990) Loss of genetic information in central nervous system tumors common to children and young adults. *Genes Chrom Cancer* 2:94–102
1500. James CD, He J, Carlbom E, Nordenskjöld M, Cavanee WK, Collins VP (1991) Chromosome 9 deletion mapping reveals interferon a and interferon b-1 gene deletions in human glial tumors. *Cancer Res* 51:1684–1688
1501. Jamjoon ZB, Saghir EL, Sadiq S, Malabarey T, Al-Khudairy (1989) Direct spread of medulloblastoma in adjacent extrameningeal tissues. *Acta Neurochir (Wien)* 97:171–176
1502. Jänisch W, Schreiber D (1977) Experimental tumors of the central nervous system. First English edition (Bigner DD, Swenberg JA eds) Upjohn, Kalamazoo
1503. Jänisch W, Horn KH, Scholtze P, Schreiber D (1968) Experimental induction of brain tumors by intracranial inoculation of Rous sarcoma virus in newborn Rhesus monkeys. *Exp Pathol (Jena)* 2:226–235
1504. Jänisch W, Schreiber D, Warzok R (1970) Frühstadien von Geschwülsten des Zentralnervensystems. Experimentellmorphologische Untersuchung. *Exp Pathol* 4:60–68
1505. Jänisch W, Güthert H, Schreiber D (1976) Pathologie der Tumoren des Zentralnervensystems. Fisher, Jena
1506. Jänisch W, Haas JF, Schreiber D, Gerlach H (1984) Primary central nervous system tumors in stillborns and infants. Epidemiological considerations. *J Neurooncol* 2:113–116
1507. Jänisch W, Schreiber D, Güthert H (1988) Tumoren des nervensystems. Fischer, Stuttgart
1508. Jannoun L, Bloom JG (1990) Long-term phycological effects in children treated for intracranial tumors. *Int J Radiat Oncol Biol Phys* 18:747–753
1509. Jansen GM, Troost D, Dingemans KP (1990) Polar spongioblastoma: an immunohistochemical and electron microscopical study. *Acta Neuropathol (Berl)* 81:228–232
1510. Jarden J, Dhawan V, Poltorak A, Posner J, Rottenberg D (1985) Positron emission tomographic measurement of blood-to-brain and blood-to-tumor transport of 82 Rb: the effect of dexamethasone and whole-brain radiation therapy. *Ann Neurol* 18:636–646
1511. Jardon-Jeghers C, Reznik M (1982) Etude immunohistochemique de 16 lymphomes primitifs du système nerveux central. *J Neurol Sci* 53:331–346
1512. Jaros E, Perry RH, Adam L, Kelly PJ, Crawford PJ, Kalbag RM, Mendelow AD, Sengupta RP, Pearson ADJ (1992) Prognostic implications of p53 protein, epidermal growth factor, receptor, and Ki-67 labelling in brain tumors. *Br J Cancer* 66:373–385
1513. Jaros E, Lunec J, Perry RH, Kelly PJ, Pearson ADJ (1993) p53 protein overexpression identifies a group of central primitive neuroectodermal tumours with poor prognosis. *Br J Cancer* 68:801–807
1514. Jastrowitz M (1870) Studien über die Encephalitis und Myelitis des ersten Kindesalters. *Arch Psychiatr Nervenkr* 3:192–213
1515. Jay V, Becker L, Squire J, Humphreys R (1993) Malignant transformation in a ganglioglioma with anaplastic neuronal and astrocytic components: report of a case with flow cytometric and cytogenetic analysis. *J Neuropathol Exp Neurol* 52:289 (abstr)
1516. Jeffreys RV, Napier J, Reynolds SH (1982) Erythropoietin levels in posterior fossa haemangioblastoma. *J Neurol Neurosurg Psychiatry* 45:264–266
1517. Jellinger K (1972) Cerebral medulloepithelioma. *Acta Neuropathol (Berl)* 22:95–101
1518. Jellinger K (1973) Primary intracranial germ cell tumors. *Acta Neuropathol (Berl)* 25:291–306
1519. Jellinger K (1977) Human central nervous system lesions following radiation therapy. *Zbl Neurochir* 38:199–218
1520. Jellinger K (1978) Glioblastoma multiforme: morphology and biology. *Acta Neurochir (Wien)* 42:5–32
1521. Jellinger K (1983) Pathologic effects of chemotherapy. In: Walker MD (ed) *Oncology of the nervous system*. Nijhoff, Boston, pp 284–340
1522. Jellinger K (1986) Vascular malformations of the central nervous system: a morphological overview. *Neurosurg Rev* 9:177–216

1523. Jellinger K (1989) Biologic behavior of meningiomas. In: Fields WS (ed) Primary brain tumors. A review of histologic classification. Springer, Berlin Heidelberg New York, pp 231–279
1524. Jellinger K, Radaszkiewicz T (1976) Involvement of the central nervous system in malignant lymphomas. *Virchows Arch Path Anat* 370:345–359
1525. Jellinger K, Slowik F (1975) Histologic subtypes and prognostic problems in meningiomas. *J Neurol* 208:279–298
1526. Jellinger K, Slowik F (1978) Beteiligung des Nervensystems bei Leukosen und malignant Lymphoman. *Zbl allg Path path Anat* 122:439–461
1527. Jellinger K, Sturm KW (1971) Delayed radiation myelopathy in man. Report of twelve necropsy cases. *J Neurol Sci* 14:389–408
1528. Jellinger K, Paulus W (1991) Mesenchymal, non meningotheial tumors of the central nervous system. *Brain Pathol* 1:79–87
1529. Jellinger K, Minauf M, Salzer-Kuntschik M (1969) Oligodendroglioma with extraneural metastases: *J Neurol Neurosurg Psychiatry* 32:249–253
1530. Jellinger K, Radaszkiewicz T, Slowik F (1975) Primary malignant lymphomas of the central nervous system in man. *Acta Neuropathol (Berl) [Suppl]* 6:95–102
1531. Jellinger K, Paulus W (1992) Primary central nervous system lymphomas – an update. *J Cancer Res Clin Oncol* 119:7–27
1532. Jellinger K, Paulus W (1995) Primary central nervous system lymphomas – new pathological developments. *J Neurooncology* 4:33–36
1533. Jen J, Harper JW, Bigner SH, Bigner DD, Papadopoulos N, Markowitz JK, Kinzler KW, Vogelstein B (1994) Deletion of p16 and p15 genes in brain tumors. *Cancer Res* 54:6353–6358
1534. Jenkin RDT (1982) Childhood ependymoma. Radiation treatment results. In: Chang CH, Housepian EM (eds) Tumors of the CNS: modern radiotherapy in multidisciplinary management. Masson, New York, pp 125–132
1535. Jenkin RDT, Boesel C, Ertel I, Evans A, Hittle R, Ortega J, Spoto R, Wara W, Wilson C, Anderson J, Leikin S, Hammond D (1987) Brain-stem tumors in childhood: a prospective randomized trial of irradiation with and without adjuvant CCNU, VCR, and prednisone: a report of the Children's Cancer Study Group. *J Neurosurg* 66:227–233
1536. Jenkins RB, Kimmel DWV, Moertel CA, Schultz CG, Scheithauer BW, Kelly PJ, Dewald JW (1989) A cytogenetic study of 53 human gliomas. *Cancer Genet Cytogenet* 39:253–279
1537. Jennings CD, Powell DE, Walsh JW, Mortara RH (1985) Suprasellar germ cell tumor with extracranial metastases. *Neurosurgery* 16:9–12
1538. Jennings MT, Gelman R, Hochberg F (1984) Intracranial germ cell tumors: natural history and pathogenesis. In: Neuwelt ED (ed) Diagnosis and treatment of pineal region tumors. Williams and Wilkins, Baltimore, pp 116–138
1539. Jennings MT, Maciunas RJ, Carver R, Bascom CC, Juneau P, Misulis K, Moses HL (1991) TGF $\beta_2$  are potential growth regulators for low-grade and malignant gliomas in vitro: evidence in support of an autocrine Hypothesis. *Int J Cancer* 49:129–139
1540. Jessen KR, Thorpe R, Mirsky R (1984) Molecular identity, distribution and heterogeneity of glial fibrillary acidic protein: an immunoblotting and immunohistochemical study of Schwann cells, satellite cells, enteric glia and astrocytes. *J Neurocytol* 13:187–200
1541. Jiddame M, Nicoli F, Diaz P, Bergvall U, Vincentelli F, Hassoun J, Salomon G (1986) Intracranial malignant lymphoma. Report of 30 cases and review of the literature. *J Neurosurg* 65:592–599
1542. Joensen P (1981) Incidence of primary intracranial neoplasms in an isolated population (the Faroese) during the period 1926–1975. *Acta Neurol Scand* 64:74–78
1543. Johannsson JH, Rehati HL, Roessmann U (1981) Gangliogliomas: pathological and clinical correlation. *J Neurosurg* 54:58–63
1544. Johnson ES, Ludwin SK (1984) Rhabdoneuroglial heterotopias of the pontine leptomeninges in trisomy 13. *Arch Pathol Lab Med* 108:906–908
1545. Johnson HA, Haymaker WE, Rubini JR, Flidner TM, Bond UP, Cronkite EP, Hughes WL (1960) A radioautographic study of human brain and glioblastoma multiforme after the in vivo uptake of tritiated thymidine. *Cancer* 13:636–642
1546. Johnson MD, Tulipan N, Whetsell Jr WO (1989) Osteoblastic meningioma of the fourth ventricle. *Neurosurgery* 24:587–590

1547. Johnson MD, Federspiel CE, Gold LJ, Moses HL (1992) Transforming growth factor-beta and transforming growth factor beta-receptor expression in human meningioma cells. *Am J Pathol* 141:633-642
1548. Johnson MR, Look AT, DeClue JE, Valentine MB, Lowy DR (1993) Inactivation of the NF1 gene in human melanoma and neuroblastoma cell lines without impaired regulation of GTPRas. *Proc Natl Acad Sci USA* 90:5539-5543
1549. Johnson MR, DeClue JE, Felzmann S, Vass WC, Xu G, White R, Lowy DR (1994) Neurofibromin can inhibit Ras-dependent growth by a mechanism independent of its GTPase-accelerating function. *Mol Cell Biol* 14:641-645
1550. Jomin M, Lesoin F, Lozes G (1985) Prognosis for arteriovenous malformations of the brain in adults based on 150 cases. *Surg Neurol* 23:362-366
1551. Jones H, Steart PV, Weller RO (1991) Spindle-cell glioblastoma or gliosarcoma? *Neuropathol Appl Neurobiol* 17:177-187
1552. Jones TR, Bigner SH, Shold SC, Jr, Eng LF, Bigner DD (1981) Anaplastic human gliomas in athymic mice. Morphology and glial fibrillary acidic protein expression. *Am J Pathol* 105:316-327
1553. Jooma R, Kendall BF (1983) Diagnosis and management of pineal tumors. *J Neurosurg* 58:654-665
1554. Jooma R, Kendall BE, Hayward RD (1984) Intracranial tumors in neonates: a report of seventeen cases. *Surg Neurol* 21:31-41
1555. Jooma R, Hayward RD, Grant DN (1984) Intracranial neoplasms during the first year of life: analysis of one hundred consecutive cases. *Neurosurgery* 14:31-41
1556. Jooma R, Torrens MJ, Bradshaw J, Brownell B (1985) Subependymomas of the fourth ventricle. Surgical treatment in 12 cases. *J Neurosurg* 62:508-512
1557. Jouvét A, Fevre-Montange M, Besançon R, Derrington E, Saint-Pierre G, Belin MF, Pialat J, Lapras C (1994) Structural and ultrastructural characteristics of human pineal gland, and pineal parenchymal tumors. *Acta Neuropathol (Berl)* 88:334-348
1558. Joyner AL, Herrup K, Auerbach BA, Davis CA, Rossant J (1991) Subtle cerebellar phenotype in mice homozygous for a targeted deletion of the En-2 homeobox. *Science* 251:1239-1243
1559. Joynt RJ, Perret GE (1961) Meningiomas in a mother and daughter. Cases without evidence of neurofibromatosis. *Neurology* 11:164-165
1560. Judge MR, Eden OB, O'Neil P (1984) Cerebral glioma after cranial prophylaxis for acute lymphoblastic leukemia. *Br Med J* 289:1038-1039
1561. Juhász P (1942) Über ein diffuses Kleinhirnoligodendrogliom und das Oligodendrogliom der hinteren Schädelgrube. *Ztschr Neurol* 174:701-714
1562. Jumenté J (1911) Les tumeurs de l'angle ponto-cérébelleux. Thèse de Paris
1563. Jurco S, Nadji M, Harvey DG, Parker JC Jr, Font RL, Morales AR (1982) Hemangioblastomas: histogenesis of the stromal cell studied by immunocytochemistry. *Hum Pathol* 13:13-18
1564. Kaba K, Tani E, Morimura T, Matsumoto T (1985) Potentiation of vincristine effect in human and murine gliomas by calcium channel blockers or calmodulin inhibitors. *J Neurosurg* 63:905-911
1565. Kadhim HJ, Gadisseux JF, Evrard P (1988) Topographical and cytological evolution of the glial phase during pre-natal development of the human brain: histochemical and electron microscopic study. *J Neuropathol Exp Neurol* 47:166-188
1566. Kadin ME, Rubinstein LJ, Nelson JS (1970) Neonatal cerebellar medulloblastoma originating from the fetal external granular layer. *J Neuropathol Exp Neurol* 29:583-600
1567. Kageyama N, Kanamori M, Yoshida J, Sugita K (1987) Pathological considerations in follow-up results of optic glioma. *Progr Exp Tumor Res* 30:100-107
1568. Kahn EA, Luros JT (1952) Hydrocephalus from overproduction of cerebrospinal fluid and experiences with other papillomas of the choroid plexus. *J Neurosurg* 9:59-67
1569. Kahn EA, Gosch HH, Seeger JF, Hicks SP (1973) Forty-five years experience with the cranio-pharyngiomas. *Surg Neurol* 1:5-12
1570. Kahn HJ, Yeger H, Kassim O (1983) Immunohistochemical and electron microscopic assessment of childhood rhabdomyosarcoma: increased frequency of diagnosis over routine histologic methods. *Cancer* 51:1897-1903
1571. Kajiwarra K, Nishizaki T, Orita T, Nakayama H, Aoki H, Ito H (1990) Silver colloid staining technique for analysis of glioma malignancy. *J Neurosurg* 73:113-117



1572. Kalimo H, Frey H, Raine CS (1979) Late-onset malignant astrocytoma in a case of multiple sclerosis. Clinical, neuropathological, virological and tissue culture studies. *Acta Neuropathol (Berl)* 46:231–234
1573. Kalimo H, Letho M, Nautö-Salonen K, Ilkanen M, Risteli J, Narva EV (1985) Characterization of the perivascular reticulin network in a case of primary brain lymphoma. *Acta Neuropathol (Berl)* 66:299–305
1574. Kallio M (1988) The incidence of intracranial gliomas in Southern Finland. *Acta Neurol Scand* 78:480–483
1575. Kalnins V, Rossi E (1965) Odontogenic craniopharyngioma. A case report. *Cancer* 18:899–906
1576. Kalyanaraman UP, Taraska JJ, Fierer JA, Elwood PW (1981) Malignant fibrous histiocytoma of the meninges: histologic, ultrastructural and immunohistochemical studies. *J Neurosurg* 55:957–962
1577. Kamb A, Gruis NA, Weaver-Feldhaus J, Liu Q, Harshman K, Tautigian SV, Stockert E, Day RS, Johnson BE, Skolnick MH (1994) A cell cycle regulator potentially involved in genesis of many tumor types. *Science* 264:436–440
1578. Kamitani H, Masuzawa H, Sato J, Kanazawa I (1987) Capillary hemangioblastoma: histogenesis of stromal cells. *Acta Neuropathol (Berl)* 73:370–378
1579. Kamitani H, Masuzawa H, Sato J, Kanazawa I (1988) Mixed oligodendroglioma and astrocytoma: fine structural and immunohistochemical studies of four cases. *J Neurol Sci* 83:219–225
1580. Kamiya K, Inagawa T, Nagasako R (1989) Malignant intraventricular meningioma with spinal metastasis through the cerebrospinal fluid. *Surg Neurol* 31:213–218
1581. Kammer KS, Perlman K, Humphreys RP, Howard NJ (1980) Clinical and surgical aspects of hypothalamic hamartoma associated with precocious puberty in a 15-month-old boy. *Childs Brain* 7:150–157
1582. Kandel E, Sangurov E, Morgunov V (1989) Cerebral and two spinal meningiomas removed from the same patient: case report. *Neurosurgery* 25:447–450
1583. Kandt RS, Shinnar S, D'Souza BJ, Singer HS, Wharam MD, Gupta PK (1984) Cerebrospinal metastases in malignant childhood astrocytomas. *J Neurooncol* 2:123–128
1584. Kandt RS, Haines JL, Smith M, Northrup H, Gardner HRJM, Short MP, Kwiatkowski DJ, Te-well A, Weber JL, Roses AD, Pericak-Vance M (1992) Linkage of an important gene locus for tuberous sclerosis to a chromosome 16 marker for polycystic kidney disease. *Nature Genet* 2:37–41
1585. Kane W, Aronson SM (1967) Gangliomatous maturation in cerebellar medulloblastoma. *Acta Neuropathol (Berl)* 9:273–279
1586. Kanno H, Kondo K, Ito S, Yamamoto I, Fujii S, Torigoe S, Sakai N, Hosaka M, Shuin T, Yao M (1994) Somatic mutations of the von Hippel-Lindau tumor suppressor gene in sporadic central nervous system hemangioblastomas. *Cancer Res* 54:4845–4847
1587. Kanter WR, Elridge R, Fabricant R, Allen JC, Koeber T (1980) Central neurofibromatosis with bilateral acoustic neurinoma: genetic, clinical and biochemical distinctions from peripheral neurofibromatosis. *Neurology* 30:851–859
1588. Kaplan MS, Hinds JW (1980) Gliogenesis of astrocytes and oligodendrocytes in the neocortical gray and white matter of the adult rat: electron microscopic analysis of light radioautographs. *J Comp Neurol* 193:711–727
1589. Kapp JP, Sanford RA (1986) Neurological deficit after carotid infusion of cisplatin and 1,3-bis(2-chloroethyl)-1-nitrosurea (BCNU) for malignant glioma: an analysis of risk factors. *Neurosurgery* 19:779–783
1590. Kappers JA (1962) Epiphysis, in Crosby EC, Humphrey T, Laner EW (eds) *Correlative anatomy of the nervous system*. New York, MacMillan, pp 268–271
1591. Karamitopoulou E, Perentes E, Diamantis I (1993) p53 protein expression in central nervous system tumors: immunohistochemical study with CM1 polyvalent and DO-7 monoclonal antibodies. *Acta Neuropathol (Berl)* 85:611–616
1592. Karamitopoulou E, Perentes E, Diamantis I, Maraziotis T (1994) Ki-67 immunoreactivity in human central nervous system tumors: a study with MIB.1 monoclonal antibody on archival material. *Acta Neuropathol (Berl)* 87:47–54
1593. Karch SB, Ulrich H (1972) Medullopithelioma: definition of an entity. *J Neuropathol Exp Neur* 31:27–53

1594. Karcioglu Z, Somren A, Mathes SJ (1987) Ectomesenchymoma: a malignant tumor of migratory neural crest (ectomesenchyme) remnants showing ganglionic, schwannian, melanocytic, and rhabdomyoblastic differentiation. *Cancer* 39:2486–2493
1595. Karim ABMF (1995) Radiation therapy and radiosurgery for brain tumors. In: Brain tumors (Kaye AN, Laws ER, eds), Churchill Livingstone, New York, pp.331–348
1596. Karim ABMF, Kralendonk JH (1991) Pitfalls and controversies in the treatment of gliomas. In: Karim ABMF, Laws ER Jr (eds) Glioma. Principles and practice in neuro-oncology. Springer, Berlin Heidelberg New York, pp 1–16
1597. Karim ABMF (1995) Radiation therapy and radiosurgery for brain tumors. In: Kaye AM, Laws ER (eds) Brain tumors. Churchill Livingstone, New York, pp 331–348
1598. Karlbom AE, James CD, Beoethius J, Cavenue WK, Collins WP, Nordenskjold M, Larsson C (1993) Loss of heterozygosity in malignant gliomas involves at least three distinct regions on chromosome 10. *Hum Genet* 92:169–174
1599. Kartner N, Riordan JR, Ling V (1983) Cell surface P-glycoprotein associated with multidrug resistance in mammalian cell lines. *Science* 221:1285–1288
1600. Kasantikul V, Brown WJ (1981) Meningiomatosis in the absence of von Recklinghausen's disease. *Surg Neurol* 15:71–75
1601. Kasantikul V, Netsky MG, Glasscock ME, Hays JW (1980) Acoustic neurilemmoma. Clinico-anatomical study of 103 patients. *J Neurosurg* 52:28–35
1602. Kaschten B, Flandroy P, Reznik M, Hainau H, Stevenaer (1995) Radiation-induced gliosarcoma. Case report and review of the literature. *J Neurosurg* 83:154–162
1603. Kastan MB, Onyekwere O, Sidransky D, Vogelstein B, Craig RW (1991) Participation of p53 protein in the cellular response to DNA damage. *Cancer Res* 51:6304–6311
1604. Katsetos CD, Burger PC (1994) Medulloblastoma. *Semin Diagn Pathol* 11:85–97
1605. Katsetos CD, Lin HM, Zacks SI (1988) Immunohistochemical and ultrastructural observations on Homer-Wright (neuroblastic) rosettes and the "pale islands" of human cerebellar medulloblastomas. *Hum Pathol* 19:1219–1227
1606. Katsetos CD, Herman MM, Frankfurter A, Gass P, Collins VP, Walker CC, Rosemberg S, Barnard RO, Rubinstein L (1989) Cerebellar desmoplastic medulloblastomas. A further immunohistochemical characterization of the reticulin-free pale islands. *Arch Pathol Lab Med* 113:1019–1029
1607. Katsetos CD, Frankfurter C, Christakos S, Mancall EL, Vlacos IN, Orich H (1993) Differential localization of class III b-tubulin isotype (bIII) and calbindin-D28k defines distinct neuronal types in the developing human cerebellar cortex. *J Neuropathol Exp Neurol* 52:655–666
1608. Katsetos CD, Krishna L and the collaborative study group (1994) Lobar pilocytic astrocytomas of the cerebral hemispheres. I. Diagnosis and nosology. *Clin Neuropathol* 13:295–305
1609. Katsetos CD, Krishna L, Friedberg E, Reidy J, Karkavelas G, Savory J (1994) Lobar pilocytic astrocytomas of the cerebral hemispheres: II. Pathobiology – morphogenesis of the eosinophilic granular bodies. *Clin Neuropathol* 13:306–314
1610. Katsetos CD, Herman MM, Krishna L, Vender JR, Vinore SA, Agamanolis DP, Schiffer D, Burger PC, Urich H (1995) Calbindin-D28K in subsets of medulloblastomas and in the human medulloblastoma cell line D283 med. *Arch Pathol Lab Med* 119:734–743
1611. Katz EL (1975) Late results of radical excision of craniopharyngiomas in children. *J Neurosurg* 42:86–90
1612. Katz HR, Goodman RL (1983) Applied radiophysics for neuro-oncology. In: Walker MD (ed) Oncology of the nervous system. Nijhoff, Boston, pp 193–222
1613. Katzman R, Pappius HM (1973) Brain electrolytes and fluid metabolism. Williams and Wilkins, Baltimore
1614. Kawakami Y, Yamada O, Tabuki K, Ohmoto T, Nishimoto A (1980) Primary intracranial choriocarcinoma. *J Neurosurg* 53:369–374
1615. Kawakami Y, Tabuchi K, Ohnishi R, Asari S, Nishimoto A (1985) Primary central nervous system lymphoma. *J Neurosurg* 62:522–527
1616. Kawamoto EH, Weidner N, Agostini RM Jr, Jaffe R (1987) Malignant ectomesenchymoma of soft tissue. Report of 2 cases and review of the literature. *Cancer* 59:1791–1802
1617. Kawamoto K, Herz F, Wooley RC, Hirano A, Kajikawa H, Koss LG (1979) Flow cytometric analysis of the DNA distribution in human brain tumors. *Acta Neuropathol (Berl)* 46:39–44

1618. Kawamoto K, Hertz F, Kajikawa H, Hirano A (1979) An ultrastructural study of cultured human meningioma cells. *Acta Neuropathol (Berl)* 46:11–15
1619. Kawamura J, Garcia JH, Kamijyo Y (1973) Cerebellar hemangioblastomas. Histogenesis of stromal cells. *Cancer* 31:1528–1540
1620. Kawano N, Yada K, Aihara M, Yagashita S (1983) Oligodendroglioma-like cells (clear cells) in ependymoma. *Acta Neuropathol (Berl)* 62:141–144
1621. Kaye AH, Morstyn G (1987) Photoradiation therapy causing selective tumor kill in a rat glioma model. *Neurosurgery* 10:408–415
1622. Kaye AH, Morstyn G, Ashcroft RG (1985) Uptake and retention of hematoporphyrin derivative in an in vivo/in vitro model of cerebral glioma. *Neurosurgery* 17:883–890
1623. Kaye AH, Morstyn G, Gardner I, Pyke K (1986) Development of a xenograft glioma model in mouse brain. *Cancer Res* 16:1367–1373
1624. Kaye AH, Morstyn G, Apuzzo ML (1988) Photoradiation therapy and its potential in the management of neurological tumors. *J Neurosurg* 69:1–14
1625. Kazner E, Stochdorph O, Wende S, Grumme T (1980) Intracranial lipoma: diagnostic and therapeutic considerations. *J Neurosurg* 52:234–245
1626. Kazumoto K, Tamura M, Hoshino H, Yuasa Y (1990) Enhanced expression of the *sis* and *c-myc* oncogenes in human meningiomas. *J Neurosurg* 72:786–791
1627. Kelly PJ (1989) Stereotactic biopsy and resection of thalamic astrocytomas. *Neurosurgery* 25:185–195
1628. Kelly PJ, Suddith RL, Hutchinson HT, Werrbach K, Haber B (1976) Endothelial growth factor present in tissue culture of CNS tumors. *J Neurosurg* 44:342–346
1629. Kelly PJ, Daumas-Duport C, Kispert DB, Kall BA, Scheithauer BW, Illig SS (1987) Imaging-based stereotaxic serial biopsies in untreated intracranial glial neoplasms. *J Neurosurg* 66:865–874
1630. Kelly PJ, Daumas-Duport C, Scheithauer BW, Kispert DB (1987) Stereotactic histologic correlations of computed tomography and magnetic resonance imaging defined abnormalities in patients with glial neoplasms. *Mayo Clin Proc* 62:450–465
1631. Kemler R, Brulet P, Schuebelen MT, Gaillard J, Jacob F (1981) Reactivity of monoclonal antibodies against intermediate filament proteins during embryonic development. *J Embryol Exp Morphol* 64:45–60
1632. Kemshead JT, Bicknell D, Greaves MF (1981) A monoclonal antibody detecting an antigen shared by neural and granulocytic cells. *Pediatr Res* 315:1281–1286
1633. Keng PC, Wheeler KT (1980) Radiation response of synchronized 9L rat brain tumor cells separated by centrifugal elutriation. *Radiat Res* 83:633–643
1634. Kennedy PGE (1982) Neural cell markers and their applications to neurology. *J Neuroimmunol* 2:35–53
1635. Kent SP, Pickering JE (1958) Neoplasms in monkeys (*macaca mulatta*): spontaneous and irradiation induced. *Cancer* 35:138–145
1636. Kepes JJ (1961) Electron microscopic studies of meningiomas. *Am J Pathol* 39:499–510
1637. Kepes JJ (1961) Observations on the formation of psammoma bodies and pseudopsammoma bodies in meningiomas. *J Neuropathol Exp Neurol* 34:255–262
1638. Kepes JJ (1971) Differential diagnostic problems of brain tumors. In: Minckler J (ed) *Pathology of the nervous system*. vol 2, McGraw-Hill, New York, pp 2219–1137
1639. Kepes JJ (1975) The fine structure of hyaline inclusions (Pseudopsammoma bodies) in meningiomas. *J Neuropathol Exp Neurol* 34:282–292
1640. Kepes JJ (1978) Transitional cell tumour of the pituitary gland developing from a Rathke's cleft cyst. *Cancer* 41:337–343
1641. Kepes JJ (1979) "Xanthomatous" lesions of the central nervous system: definition, classifications, and some recent observations. In: Zimmerman HM (ed) *Progress in neuropathology* vol 4. Raven, New York, pp 179–213
1642. Kepes JJ (1982) Meningiomas. Biology, pathology and differential diagnosis. Masson, New York
1643. Kepes JJ (1989) History and diagnosis of meningiomas. In: Fields WS (ed) *Primary brain tumors. A review of histologic classifications*. Springer, Berlin Göttingen New York, pp 217–230

1644. Kepes JJ (1993) Pleomorphic xanthoastrocytoma: the birth of a diagnosis and a concept. *Brain Pathol* 3:269–274
1645. Kepes JJ (1994) Lipidized meningotheial tumor cells in “xanthomatous” meningioma express macrophage antigens. *J Neuropathol Exp Neurol* 53:384–388
1646. Kepes JJ, Kepes M (1975) Lymphoreticular proliferative disorders of the CNS and other organs: analogies and differences. *Acta Neuropathol (Berl)* [Suppl] VI:75–80
1647. Kepes JJ, Rubinstein LJ (1981) Malignant gliomas with heavily lipidized (foamy) tumor cells: a report of three cases with immunoperoxidase study. *Cancer* 47:2451–2459
1648. Kepes JJ, Kepes M, Slowik F (1973) Fibrous xanthomas and xanthosarcomas of the meninges and the brain. *Acta Neuropathol (Berl)* 23:187–199
1649. Kepes JJ, Rubinstein LJ, Eng LF (1978) Meningocerebral xanthoastrocytoma. A distinctive glioma of young subjects presumably originating from subpial astrocytes, with relatively favorable prognosis. A study of ten cases. *Proceedings of the 8th International Congress on Neuropathology*, 24–29 September, Washington, p 641
1650. Kepes JJ, Rubinstein LJ, Eng LF (1979) Pleomorphic xanthoastrocytoma: a distinctive meningocerebral glioma of young subjects with relatively favorable prognosis. A study of 12 cases. *Cancer* 44:1839–1852
1651. Kepes JJ, Lewis RC, Vergara GG (1980) Cerebellar astrocytoma invading the musculature and soft tissue of the back. Case report. *J Neurosurg* 52:414–418
1652. Kepes JJ, Fulling KH, Garcia JH (1982) The clinical significance of “adenoid” formations of neoplastic astrocytes, imitating metastatic carcinoma, in gliosarcomas: a review of five cases. *Clin Neuropathol* 1:139–150
1653. Kepes JJ, Goldware S, Leoni R (1983) Meningioma with pseudoglandular pattern. *J Neuropathol Exp Neurol* 42:61–68
1654. Kepes JJ, Rubinstein LJ, Chiang H (1984) The role of astrocytes in the formation of cartilage in gliomas. An immunohistochemical study of four cases. *Am J Pathol* 117:471–483
1655. Kepes JJ, Belton K, Roessmann U, Ketcherside WJ (1985) Primary neuroectodermal tumors of the cauda equina in adults with no detectable primary intracranial neoplasm – three case studies. *Clin Neuropathol* 4:1–11
1656. Kepes JJ, Chen WY-K, Connors MH, Vogel FS (1988) ‘Chordoid’ meningeal tumors in young individuals with peritumoral lympho-plasmacellular infiltrates causing systemic manifestations of the Castleman syndrome. *Cancer* 62:391–406
1657. Kepes JJ, Rubinstein LJ, Ansbecher L, Schreiber DJ (1989) Histopathological features of recurrent pleomorphic xanthoastrocytoma: further corroboration of the glial nature of the neoplasm. A study of three cases. *Acta Neuropathol (Berl)* 78:187–199
1658. Kepes JJ, Whittaker CK, Watson K, Morantz RA, Millett R, Clough CA, Oxley DR (1989) Cerebellar astrocytomas in elderly patients with very long preoperative histories: report of three cases. *Neurosurgery* 25:258–264
1659. Kernohan JW, Fletcher-Kernohan EM (1935) Ependymomas. A study of 109 cases. *Proc Assoc Res Nerv Ment Dis (Baltimore)* 16:182–209
1660. Kernohan JW, Sayre GP (1952) Tumors of the cranial nervous system. AFIP, Washington DC
1661. Kernohan JW, Mabon RF, Svien HJ, Adson AW (1949) Simplified classification of gliomas. *Proc Staff Meet Mayo Clin* 24:71–75
1662. Kersall MA, Lewis P (1964) Mast cells in the brain. *Fed Proc* 23:1107–1112
1663. Kershman J (1938) The medulloblast and the medulloblastoma; a study of human embryos. *Arch Neurol Psych* 40:937–967
1664. Kersting G (1968) Tissue culture of human gliomas. *Progr Neurol Surg* 2:165–202
1665. Kersting G, Finkemeyer H (1958) Das Wachstum menschlichen Neurinomgewebes in vitro. *Zbl Neurochir* 18:2–11
1666. Kersting G, Lennartz H (1957) In vitro cultures of human meningioma tissue. *J Neuropathol Exp Neurol* 16:507–513
1667. Kholodov YA (1966) The effects of electromagnetic and magnetic fields on the central nervous system, NASA technical translation, 1967. Moscow, Academy of Science USSR
1668. Kibel A, Lliopulos O, DeCaprio JA, Kaelin Jr WG (1995) Binding of the von Hippel-Lindau tumor suppressor protein to elongin B and C. *Science* 269:1444–1446
1669. Kies MS, Kennedy PS (1979) Central nervous system involvement in Ewing’s sarcoma. *Ann Intern Med* 89:226–227

1670. Kiessling M, Kleihues P, Gessaga E, Mundinger F, Ostertag ChB, Weigel K (1984) Morphology of intracranial tumours and adjacent brain structures following interstitial iodine-125 radiotherapy. *Acta Neurochir (Wien)* 33:281-289
1671. Kikuchi K, Neuwelt EA (1983) Presence of immunosuppressive factors in brain-tumor cyst fluid. *J Neurosurg* 59:790-799
1672. Kim JA, Elkom D, Linn ML, Constable WC (1980) Optimum dose of radiotherapy for chemodectomas of the middle ear. *Int J Radiat Oncol Biol Phys* 6:815-819
1673. Kim JH, Duncan C, Manuelidis EE (1988) Congenital cerebellar medulloblastoma. *Surg Neurol* 23:75-81
1674. Kim KJ, Li B, Winer J, Armanini M, Gillett N, Philips HS, Ferrara N (1993) Inhibition of vascular endothelial growth factor-induced angiogenesis suppresses tumor growth in vivo. *Nature* 362:841-844
1675. Kim SV, Moretto G, Shin DM, Lee VM (1985) Modulation of antigenic expression in cultured adult human oligodendrocytes by derivatives of adenosine 3,5-cyclic monophosphate. *J Neurol Sci* 69:81-91
1676. Kim TS, Halliday AL, Hedley-Whyte ET, Convery K (1991) Correlates of survival and the Daumas-Duport grading system for astrocytomas. *J Neurosurg* 74:27-37
1677. Kim YH, Fayos JV (1978) Intracranial ependymomas. *Radiology* 124:805-808
1678. Kimler BF, Henderson SD (1982) Cyclic response of cultured 9L cells to radiation. *Radiat Res* 91:155-168
1679. Kimmel DW, Shapiro JR, Shapiro WR (1987) In vitro drug sensitivity testing in human gliomas. *J Neurosurg* 66:161-171
1680. Kimura N, Sasano N, Ishioka K (1986) Use of formaldehyde-induced fluorescence for cytological diagnosis of pheochromocytoma. *Acta Pathol Japon* 36:1049-1054
1681. Kimura T, Budka H, Soler-Federspiel S (1986) An immunocytochemical comparison of the glia-associated proteins glial fibrillary acidic protein (GFAP) and S-100 protein (S100P) in human brain tumours. *Clin Neuropathol* 5:21-27
1682. Kindblom LG, Jacobsen GK, Jacobsen M (1982) Immunohistochemical investigation of tumors of supposed fibroblastic-histiocytic origin. *Hum Pathol* 13:834-840
1683. Kingston JE, Plowman PN, Hungerford JL (1985) Ectopic intracranial retinoblastoma in childhood. *Br J Ophthalmol* 69:742-748
1684. Kinney TE, Adams RD (1943) Reticulum cell sarcoma of the brain. *Arch Neurol* 50:552-564
1685. Kinsella TJ, Weichselbaum RR, Sheline GE (1980) Radiation injury of cranial and peripheral nerves. In: Gilbert HA, Kagan AR (eds) *Radiation damage to the nervous system*. Raven, New York, pp 145-154
1686. Kinzler KW, Bigner BS, Bigner DD, Trent JM, Law ML, O'Brien SJ, Wong HJ, Vogelstein B (1987) Identification of an amplified, highly expressed gene in a malignant glioma. *Science* 236:70-73
1687. Kirch ME, Hammerling U (1981) Immunotherapy of murine leukemias by monoclonal antibody. I Effect of passively administered antibody on growth of transplanted tumor cells. *J Immunol* 127:805-810
1688. Kirkpatrick PJ, Honavar M, Janota I, Polkey CE (1993) Control of temporal lobe epilepsy following en bloc resection of low-grade tumors. *J Neurosurg* 78:19-25
1689. Kirsch WM, Hodges FJ (1966) An intramedullary epidermal inclusion cyst of the thoracic cord associated with a previously repaired meningocele. *J Neurosurg* 24:1018-1020
1690. Kirsch WM, Schultz D, Leitner JW (1967) The effect of prolonged ischemia upon regional energy reserves in the experimental glioblastoma. *Cancer Res* 27:2212-2220
1691. Kishikawa M, Tsuda N, Enjii H, Nishimori I, Yokohama H, Kihara M (1986) Glioblastoma with sarcomatous component associated with mixoid change. A histochemical, immunohistochemical and electron microscopic study. *Acta Neuropathol (Berl)* 70:44-52
1692. Kitanaka C, Shitara N, Nakagomi T, Nakamura H, Genka S, Nakagawa K, Akanuma A, Aoyama H, Takakura K (1989) Postradiation astrocytoma. Report of two cases. *J Neurosurg* 70:469-474
1693. Kito A, Yoshida J, Gageyama N, Kojima N, Yagi K (1989) Liposomes coupled with monoclonal antibodies against glioma-associated antigen for targeting chemotherapy of glioma. *J Neurosurg* 71:382-387

1694. Kivelä T, Tarkkanen A (1986) S-100 protein in retinoblastoma revisited. An immunohistochemical study. *Acta Ophthalmol* 64:664–670
1695. Klatzo I (1967) Presidential address: Neuropathological aspects of brain edema. *J Neuropathol Exp Neurol* 26:1–14
1696. Klatzo I (1979) Cerebral edema and ischemia. In: Smith WT, Cavanagh JB (eds) Recent advances in neuropathology vol 1. Churchill, Livingstone, pp 27–39
1697. Kleihues P, Bigner DD (1981) Tumours of the nervous system. In: Davison AN, Thompson RHS (eds) The molecular basis of neuropathology. Arnold, London, pp 81–103
1698. Kleihues P, Rajewsky MF (1984) Clinical neuro-oncogenesis: role of structural DNA modifications, DNA repair and neural target cell population. *Progr Exp Tumor Res*, 27:1–16
1699. Kleihues P, Matsumoto S, Wechsler W, Zülch KJ (1968) Morphologie und Wachstum der mit Äthylnitrosoharnstoff transplazentar erzeugten Tumoren des Nervensystems. *Verh Dtsch Ges Path* 52:372–379
1700. Kleihues P, Shibata T, Wiestler OD, Aguzzi A (1990) Morphological and immunohistochemical analysis of 330 medulloblastomas. Biwako Symposium on Brain Tumor Pathology, 9–10 September, Siwako, Japan, pp 25
1701. Kleihues P, Aguzzi A, Wiestler OD (1990) Cellular and molecular aspects of neurocarcinogenesis. *Toxicol Pathol* 18:193–203
1702. Kleihues P, Burger PC, Scheithauer BW (1993) Histological typing of tumours of the central nervous system. WHO Blue Book, 2nd edn. Springer, Berlin Heidelberg New York
- 1702a. Kleihues P, Burger PC, Scheithauer BW (1993) The new WHO classification of brain tumours. *Brain Pathol* 3:255–268
1703. Klein G (1953) Ueber einige besondere Ependymome. *Zbl Neurochir* 13:150–158
1704. Klein G (1988) Oncogenes and tumor suppressor genes. *Rev Oncol* 1:427–437
1705. Klein P, Rubinstein LJ (1989) Benign symptomatic glial cysts in the pineal gland: a report of 7 cases and review of the literature. *J Neurol Neurosurg Psychiatry* 52:991–995
1706. Kleinert R (1991) Immunohistochemical characterization of primitive neuroectodermal tumors and their possible relationship to the stepwise ontogenetic development to the central nervous system. *Acta Neuropathol (Berl)* 82:502–507
1707. Kleinman GM, Schoene WC, Walshe TM III, Richardson EP Jr (1978) Malignant transformation in benign cerebellar astrocytoma: case report. *J Neurosurg* 49:111–118
1708. Kleinman GM, Liszczak T, Tarlou E, Richardson EP (1980) Microcystic variant of meningioma. A light-microscopic and ultrastructural study. *Am J Surg Pathol* 4:383–398
1709. Kleinman GM, Hochberg FH, Richardson EP (1981) Systemic metastases from medulloblastoma: report of two cases and review of the literature. *Cancer*, 48:2296–2309
1710. Kleinman GM, Young RH, Scully RE (1984) Ependymoma of the ovary: report of three cases. *Hum Pathol* 15:632–638
1711. Kleinman HK, Klebe RJ, Martin GR (1981) Role of collagenous matrices in the adhesion and growth of cells. *J Cell Biol* 88:473–475
1712. Kleinsasser O (1957) Die Tumoren des Glomus Jugulare und der anderen nicht chromaffinen Paraganglien im Bereich der Schädelbasis. *Zbl Neurochir* 17:155–168
1713. Kleinsasser O, Friedmann G (1959) Über Neurinome des Nervus facialis. *Zbl Neurochir* 19:49–59
1714. Kleinschmidt-DeMaster BK, Avakian JJ (1985) Wallenberg syndrome caused by CSF metastasis from malignant intraventricular meningioma. *Clin Neuropathol* 4:214–219
1715. Kleinschmidt-DeMasters BK, Geier JM (1989) Pathology of high-dose intraarterial BCNU. *Surg Neurol* 31:435–443
1716. Klériga E, Sher JH, Nallainathan SK, Stein S, Sacher M (1978) Development of cerebellar malignant astrocytoma at site of medulloblastoma treated 11 years earlier. Case report. *J Neurosurg* 49:445–449
1717. Kline KT, Damyanov I, Katz SM, Schmidek H (1979) Pinealoblastoma: an electron microscopic study. *Cancer* 44:1692–1699
1718. Klose HH (1961) Deutung des Zusammenhanges zwischen elastischen Fasern, Gefässen und Psammomkörperbildung in Meningeomen. *Acta Neurochir (Wien)* 9:359–366
1719. Kluin P (1994) bcl-6 in lymphoma – sorting out a wastebasket? *N Engl J Med* 331:116–118
1720. Knigge KM, Scott DE (1970) Structure and function of the median eminence. *Am J Anat* 129:223–244

1721. Krijten RR, Bunin GR, Nass CC, Meadows AT (1990) Gestational and familial risk factors for childhood astrocytoma: result of a case-control study. *Cancer Res* 50:2608–2612
1722. Knowles JF (1982) The effect of X-radiation given after neonatal administration of ethylnitrosourea on incidence of induced nervous system tumours. *Neuropathol Appl Neurobiol* 8:265–276
1723. Knuckley NW, Stoll J Jr, Epstein MH (1989) Intracranial and spinal meningiomas in patients with breast carcinoma: case reports. *Neurosurgery* 25:112–117
1724. Knudson AG (1971) Mutation and cancer: statistical study of retinoblastoma. *Proc Natl Acad Sci USA* 68:820–823
1725. Knudson AG (1986) Genetics of human cancer. *Ann Rev Genet* 20:231–251
1726. Knudson W, Biswas C, Li X-Q, Nemec RE, Toole BP (1989) The role and regulation of tumor-associated hyaluronan. *Ciba Found Symp* 143:150–169
1727. Kobayashi S, Yamadori I, Miki H, Ohmori M (1987) Idiopathic arteriosclerotic cerebral calcification (Fahr's disease): an electron microscopic study. *Acta Neuropathol (Berl)* 73:62–66
1728. Kobayashi T, Toshida J, Kageyama N (1978) A case of recurrent Rathke's cleft cyst. *Neurol Surg* 6:437–444
1729. Kobayashi T, Kageyama N, Ohara K (1981) Internal irradiation for cystic craniopharyngioma. *J Neurosurg* 55:896–903
1730. Kobayashi T, Yoshida J, Kida Y (1989) Bilateral germ cell tumors involving the basal ganglia and thalamus. *Neurosurgery* 25:579–583
1731. Kochi N, Budka H (1987) Contribution of histiocytic cells to sarcomatous development of the gliosarcoma. *Acta Neuropathol (Berl)* 73:124–130
1732. Kochi N, Tani E, Kaba K, Natsume S (1984) Immunohistochemical study of fibronectin in hemangioblastomas and emangiopericytomas. *Acta Neuropathol (Berl)* 64:229–233
1733. Kochi N, Budka H, Radaszkiewicz T (1986) Development of stroma in malignant lymphomas of the brain compared with epidural lymphomas. An immunohistochemical study. *Acta Neuropathol (Berl)* 71:125–129
1734. Kocks W, Kalff R, Reinhardt V, Grote W, Hilke J (1989) Spinal metastasis of pilocytic astrocytoma of the chiasma opticum. *Childs Nerv Syst* 5:118–120
1735. Koeleveld RF, Cohen AR (1991) Primary embryonal-cell carcinoma of the parietal lobe. *J Neurosurg* 75:468–471
1736. Koller KK, Dillon WP (1992) Dysembryoplastic neuroepithelial tumors: MR appearance. *AJNR* 13:1319–1325
1737. Koeppen AH, Cassidy RJ (1981) Oligodendroglioma of the medulla oblongata in a neonate. *Arch Neurol* 38:520–523
1738. Koestner A, Swenberg JA, Wechsler W (1971) Transplacental production with ethylnitrosourea of neoplasm of the nervous system in Sprague-Dawley rats. *Am J Pathol* 63:37–56
1739. Koide O, Iwai S (1981) An ultrastructural study on germinoma cells. *Acta Pathol Jpn* 31:755–766
1740. Koide O, Watanabe Y, Sato K (1980) A pathological survey of intracranial germinoma and pinealoma in Japan. *Cancer* 45:2119–2130
1741. Kokkoris CP (1983) Leptomeningeal carcinomatosis. How does cancer reach the pia-arachnoid? *Cancer* 51:154–160
1742. Komuro I, Schalling M, Jahn L, Bodmer R, Jenkins NA, Copeland NG, Izumo S (1993) Gtx: a novel murine homeobox-containing gene, expressed specifically in glial cells of the brain and germ cells of testis, has a transcriptional repressor activity in vitro for a serum-inducible promoter. *EMBO J* 4:1387–1401
1743. Kondo S, Morimura T, Takeuchi (1995) Combination therapy with cisplatin and nifedipine inducing apoptosis in multidrug-resistant human glioblastoma cells. *J Neurosurg* 82:469–474
1744. Kondziolka D, Bilbao JM (1988) Mixed ependymoma-astrocytoma (subependymoma?) of the cerebral cortex. *Acta Neuropathol (Berl)* 76:633–637
1745. Kondziolka D, Dade Lunsford L, Flickinger JC (1991) The role of radiosurgery in the management of chordoma and chondrosarcoma of the cranial base. *Neurosurgery* 29:38–46
1746. Kondziolka D, Lunsford LD, Chassen D (1992) Radiobiology of radiosurgery: part II. The rat C6 glioma model. *Neurosurgery* 31:280–288
1747. Kopelson G (1982) Cerebellar glioblastoma. *Cancer* 50:308–311

1748. Kopelson G, Linggood RM, Kleinmann GM, Douchette J, Wang CC (1980) Management of intramedullary spinal cord tumors. *Radiology* 135:473–479
1749. Kopelson G, Linggood RM, Kleinman GM (1983) Medulloblastoma: the identification of prognostic subgroups and implications for multimodality management. *Cancer* 51:312–319
1750. Koppel H, Pilkington GJ, Lantos PL (1988) Tumorigenicity of six clones of a cultured neoplastic cell line derived from a spontaneous murine astrocytoma: morphology and immunocytochemistry of tumours. *J Neurol Sci* 83:227–242
1751. Kordek R, Biernat W, Sapieja W, Alwasiak J, Liberski PP (1995) Pleomorphic xanthoastrocytoma with a gangliomatous component: an immunohistochemical and ultrastructural study. *Acta Neuropathol* 89:194–197
1752. Korf HW, Moller M, Gery I, Zigler JS, Klein DC (1985) Immunocytochemical demonstration of retinal S-antigen in the pineal organ of four mammalian species. *Cell Tissue Res* 239:81–85
1753. Korf HW, Czerwionka M, Reiner J, Schachenmayr W, Schalken JJ, de Grip W, Gery I (1987) Immunocytochemical evidence of molecular photoreceptor markers in cerebellar medulloblastomas. *Cancer* 60:1763–1766
1754. Kornblith PL, Szytko PE (1978) Variations in response of human brain tumors to BCNU in vitro. *J Neurosurg* 48:580–586
1755. Kornblith PL, Dohan FC Jr, Wood WC, Whitman BO (1974) Human astrocytoma: serum-mediated immunologic response. *Cancer* 33:1512–1519
1756. Kornblith PL, Smith BH, Leonard LA (1981) Response of cultured human brain tumours to nitrosoureas: correlations with clinical data. *Cancer* 47:255–265
1757. Kornfeld M (1986) Granular cell glioblastoma: a malignant granular cell neoplasm of astrocytic origin. *J Neuropathol Exp Neurol* 45:447–462
1758. Korr H (1980) Proliferation of different cell types in the brain. *Adv Anat Embryol Cell Biol* 61:1–72
1759. Korr H, Schultre B, Maurer W (1973) Autoradiographic investigations of glial proliferation in the brain of adult mice. The DNA synthesis place of neuroglia and endothelial cells. *J Comp Neurol* 150:169–176
1760. Korr H, Schultre B, Maurer W (1975) Autoradiographic investigations of glial proliferation in the brain of adult mice. II Cycle time and mode of proliferation of neuroglia and endothelial cells. *J Comp Neurol* 160:477–490
1761. Kosnick EJ, Boesel CP, Bay J, Sayers MP (1978) Primitive neuroectodermal tumors of the central nervous system in children. *J Neurosurg* 48:741–746
1762. Kostovic L, Krmpotic-Nemanic J, Kelovic A (1975) The early development of glia in human neocortex. *Rad Jug Acad Znan Unijet Nat Sci Series* 17:155–159
1763. Kosyca B, Moore L, Byard RW (1993) Lethal manifestations of neurofibromatosis type 1 in childhood. *Pediatr Pathol* 13:573–581
1764. Kovacs K, Horvath E, Stratmann IE, Ezrin C (1974) Cytoplasmic microfilaments in the anterior lobe of the human pituitary gland. *Acta Anat* 87:414–426
1765. Kovelich JJ, Grigsby PW, Shepard MJ, Fineberg BB, Thomas PR (1990) Radiation therapy for gliomas of the optic nerve and chiasm. *Int J Radiat Oncol Biol Phys* 18:927–932
1766. Kozmik Z, Sure U, Rüedi D, Busslinger M, Aguzzi A (1995) Deregulated expression of PAX5 in medulloblastoma. *Proc Natl Acad Sci USA* 92:5709–5713
1767. Kraig RP, Dong L, Thisted R, Jaeger CB (1991) Spreading depression increases immunohistochemical staining of glial fibrillary acidic protein. *J Neurosci* 11:2187–2198
1768. Krainer L (1935) Die Hirn- und Rückenmarkslipome. *Virchows Arch* 295:107–122
1769. Krämer G (1982) Hirntumor nach Trauma: Literaturübersicht und Begutachtungsproblematik. *Akt Neurol* 9:112–120
1770. Kramer S, Southard M, Mansfield CM (1968) Radiotherapy in the management of cranio-pharyngiomas. Further experiences and late results. *Am J Radiol* 103:44–52
1771. Kramer S, Southard ME, Mansfield CM (1972) Radiation effects and tolerance of the central nervous system. *Front Radiat Ther Oncol* 6:332–345
1772. Kramer S, Meadows AT, Jarrett P (1983) Incidence of childhood cancer: experience of a decade in a population-based registry. *J Natl Cancer Inst* 70:49–55



1773. Kramer S, Ward E, Meadows AT, Malone KE (1987) Medical and drug risk factors associated with neuroblastoma: a case-control study. *J Natl Cancer Inst* 78:797-804
1774. Krath F, Faist M, Warncke P, Volk B, Ostertag C (1995) Interstitial radiosurgery of low grade gliomas. *J Neurosurg* 82:418-429
1775. Kraus JA, Bollen C, Wolf HK, Neumann J, Kindermann D, Fimmers R, Forster F, Baumann A, Schlegel U (1994) TP53 alterations and clinical outcome in low grade astrocytomas. *Genes Chrom Cancer* 10:143-149
1776. Kraus JA, Koopmann J, Kaskel P, Maintz D, Brandner S, Schramm J, Louis DN, Wiestler OD, von Deimling A (1995) Shared allelic losses on chromosomes 1p and 19q suggest a common origin of oligodendroglioma and oligoastrocytoma. *J Neuropathol Exp Neurol* 54:91-95
1777. Krayenbühl H, Yasargil G (1958) Das Kleinhirnhämangiom. *Schweiz Med Wschr* 88:99-104
1778. Kreth FW, Faist M, Warnke PC, Robner R, Volk B, Ostertag CB (1995) Interstitial radiosurgery of low-grade gliomas. *J Neurosurg* 82:418-429
1779. Kretschmar CS, Tartell NJ, Kupsky W, Lavally BL, Loeffler JS, Wolfe L, Strand R, Scott RM, Sallan SE (1989) Pre-irradiation chemotherapy for infants and children with medulloblastoma: a preliminary report. *J Neurosurg* 71:820-825
1780. Kricheff II, Becker M, Schenk SA, Taveras JM (1964) Intracranial ependymomas; factors influencing prognosis. *J Neurosurg* 21:7-14
1781. Kristt DA, Reedy E, Yarden Y (1993) Receptor tyrosine kinase expression in astrocytic lesions: Similar features in gliosis and glioma. *Neurosurgery* 33:106-115
1782. Kros JM, van Eden CG, van der Werf AJM, Uylings HBM (1988) Oligodendroglioma: a comparison of two grading systems. *Cancer* 61:2251-2259
1783. Kros JM, van Eden CG, Stefanko SZ, Waayer-van Batenburg M, van der Kwast ThH (1991) Prognostic implications of glial fibrillary acidic protein containing cell types in oligodendrogliomas. *Cancer* 66:1204-1212
1784. Kros JM, Jong AAW, Van der Kwast T H (1992) Ultrastructural characterization of transitional cells in oligodendrogliomas. *J Neuropathol Exp Neurol* 51:186-193
1785. Kros JM, Van Eden CG, Vissers CJ, Mulder Aa, Van der Kwast Th H (1992) Prognostic relevance of DNA flow cytometry in oligodendroglioma. *Cancer* 69:1791-1798
1786. Kros JM, Pieterman H, Van Eden CG, Avezaat CJJ (1994). Oligodendroglioma: The Rotterdam-Dijkzigt experience. *Neurosurgery* 34:959-966
1787. Krouwer HJG, Davis RL, Silver P, Prados M (1991) Gemistocytic astrocytomas. A reappraisal. *J Neurosurg* 74:399-406
1788. Krouwer HJG, Davis RL, McDermott MW, Hoshino T, Prados MD (1993) Gangliogliomas: a clinicopathological study of 25 cases and review of the literature. *J Neurooncol* 17:139-154
1789. Krücke W (1940) Über das Vorkommen von Knochengewebe in Gehirnarterien. *Arch Psychiatr* 111:233-250
1790. Krumm A, Groudine M (1995) Tumor suppression and transcription elongation: the dire consequences of changing partners. *Science* 269:1400-1401
1791. Krupp JM (1976) Nine-years mortality experience in proton-exposed *Macaca mulatta*. *Radiat Res* 67:244-251
1792. Kruse F (1960) Meningeal tumors with extracranial metastasis. A clinicopathologic report of 2 cases. *Neurology* 10:197-201
1793. Kubota T, Hirano A, Yamamoto S, Kajikawa K (1984) The fine structure of psammoma bodies in meningocytic whorls. *J Neuropathol Exp Neurol* 43:37-44
1794. Kubota T, Sato K, Yamamoto S, Hirano A (1984) Ultrastructural study of formation of psammoma bodies in fibroblastic meningioma. *J Neurosurg* 60:512-517
1795. Kubota T, Hirano A, Sato K, Yamamoto S (1984c) Fine structure of psammoma bodies in meningocytic whorls. Further observations. *Arch Pathol Lab Med* 108:752-754
1796. Kubota T, Hirano A, Sato K, Yamamoto S (1985b) Fine structure of psammoma bodies at the outer aspect of blood vessels in meningioma. *Acta Neuropathol (Berl)* 66:163-166
1797. Kubota T, Hirano A, Sato K, Yamamoto S (1985) The fine structure of astroblastoma. *Cancer* 55:745-750
1798. Kubota T, Yamashima T, Hasegawa M, Kida S, Hayashi M, Yamamoto S (1986) Formation of psammoma bodies in meningocytic whorls. Ultrastructural study and analysis of calcified material. *Acta Neuropathol (Berl)* 70:262-268

1799. Kuchelmeister K, Bergmann M, Wild K von, Hochreuter D, Busch G, Gullotta F (1993) Desmoplastic ganglioglioma report of two non-infantile cases. *Acta Neuropathol (Berl)* 85:199–204
1800. Kudo H, Oi S, Tamaki N, Nishida Y, Matsumoto S (1990) Ependymoma diagnosed in the first year of life in Japan, in collaboration with the International Society for Pediatric Neurosurgery. *Childs Nerv Syst* 6:375–378
1801. Kudo H, Mio T, Kokunai T, Tamaki, Sumino K, Matsumoto S (1990) Quantitative analysis of glutathione in human brain tumors. *J Neurosurg* 72:610–615
1802. Kuerbitz SJ, Plunkett BS, Walsh WV, Kastan MB (1992) Wild-type p53 is a cell cycle checkpoint determinant following irradiation. *Proc Natl Acad Sci USA* 89:7491–7495
1803. Kuhajda FP, Mendelsohn G, Taxy JB, Long DM (1981) Pleomorphic xanthoastrocytoma: report of a case with light and electron microscopy. *Ultrastruct Pathol* 2:25–32
1804. Kumabe T, Sohma Y, Kayama T, Yoshimoto T, Yamamoto T. (1992) Amplification of alpha-platelet-derived growth factor receptor gene lacking an exon coding for a portion of the extracellular region in a primary brain tumor of glial origin. *Oncogene* 7:627–633
1805. Kumanishi T, Ikuta F, Yamamoto T (1973) Brain tumors induced by Rous sarcoma virus, Schmidt-Ruppin strain III. Morphology of brain tumours induced in adult mice. *J Natl Cancer Inst* 50:95–109
1806. Kumanishi T, Washiyama K, Watabe K, Sekiguchi K (1985) Glial fibrillary acid protein in medulloblastomas. *Acta Neuropathol (Berl)* 67:1–5
1807. Kumanishi T, Washiyama K, Saito T, Nishiyama A, Abe S, Tanaka T (1986) Primary malignant lymphoma of the brain: an immunohistochemical study of 8 cases using a panel of monoclonal and heterologous antibodies. *Acta Neuropathol (Berl)* 71:190–196
1808. Kumanishi T, Washiyama K, Nishiyama A, Abe S (1988) Primary malignant lymphoma of the brain: demonstration of immunoglobulin gene rearrangements. *Clin Neuropathol* 7:180
1809. Kumar ARV, Hoshino T, Wheeler KT, Barker M, Wilson CB (1974) Comparative rates of dead tumor cell removal from brain, muscle, subcutaneous tissue and peritoneal cavity. *J Natl Cancer Inst* 52:1751–1755
1810. Kumar P, Kumar S, Marsden HB et al (1980) Weibel-Palade bodies in endothelial cells as a marker for angiogenesis in brain tumors. *Cancer Res* 40:2010–2019
1811. Kumar PP, Good RR, Skultety FM, Leibrock LG, Severson GS (1987) Radiation-induced neoplasms of the brain. *Cancer* 59:1274–1284
1812. Kumar PP, Good RR, Patil AA, Leibrock LG (1989) Permanent high-activity Iodine-125 in the management of petroclival meningiomas: case reports. *Neurosurgery* 25: 436–442
1813. Kumar R, Tekkök JM, Jones RAC (1990) Intracranial tumors in the first 18 months of life. *Childs New Syst* 6:371–374
1814. Kumpulainen T, Korhonen LK (1982) Immunohistochemical localization of carbonic anhydrase isoenzyme C in central and peripheral nervous system of the mouse. *J Histochem Cytochem* 30:283–292
1815. Kumpulainen T, Dahl D, Korhonen LK, Nyström SHM (1983) Immunolabeling of carbonic anhydrase isoenzyme C and glial fibrillary acidic protein in paraffin embedded tissue sections of human brain and retina. *J Histochem Cytochem* 31:879–886
1816. Kun LE (1983) Patterns of failure in tumors of the central nervous system. In: *Cancer Treatment Symposia, Proc Workshop on Patterns of failure after cancer therapy*, pp 285–294
1817. Kun LE, Mulhern RK, Crisco JJ (1983) Quality of life in children treated for brain tumors. *J Neurosurg* 58:1–6
1818. Kun LE, Gajjar A, Muhlbauer M, Heideman RL, Sanford R, Brenner M, Walter A, Langston J, Jenkins J, Facchini S (1995) Stereotactic injection of herpes simplex thymidine kinase vector producer cells (PA317-G1TK1SvNa7) and intravenous ganciclovir for the treatment of progressive or recurrent primary supratentorial pediatric malignant brain tumors. *Hum Gen Ther* 6:9 1231–1255
1819. Kung PC, Lee JC, Bakay L (1969) Vascular invasion by glioma cells in man: an electron microscopic study. *J Neurosurg* 31:339–345
1820. Kunishio K, Ohmoto T, Matsuhisa T, Maeshiro T, Furuta T, Matsumoto K (1994). The significance of nucleolar organizer region (AgNOR) score in predicting meningioma recurrence. *Cancer* 73:2200–2205

1821. Kunz J, Gottschalk J, Jänisch W, Schulz W (1986) Zellproliferation und Expression des säuren Gliafaserproteins (GFAP) in Hirntumoren. *Acta Histochem* 80:53–61
1822. Kuppper MC, Hamon MF, Bodmer S, Fontana A, De Tribolet N (1988) The glioblastoma-derived T cell suppressor factor/transforming growth factor B 2 inhibits the generation of lymphokine activated killer (LAK) cells. *Int J Cancer* 42:562–567
1823. Kurland LT (1958) The frequency of intracranial and intraspinal neoplasms in the resident population of Rochester, Minnesota. *J Neurosurg* 15:627–641
1824. Kurland LT, Schoenberg BS, Annegers JE, Okazaki H, Molgaard CA (1982) The incidence of primary intracranial neoplasms in Rochester, Minnesota, 1935–1977. *Ann NY Acad Sci* 381:6–16
1825. Kurman RJ, Scandino PT (1981) Alpha-fetoprotein and human chorionic gonadotropin in ovarian and testicular germ cell tumors. In: De Lellis RA (ed) *Diagnostic immunohistochemistry*. Masson, New York, pp 277–298
1826. Kuroki M, Tanaka R, Hondo H (1987) Antitumor effect of interferon combined with hyperthermia against experimental brain tumors. *Int J Hyperthermia* 3:527–534
1827. Kurpad SN, Friedman HS, Archer GE, McLendon RE, Petros WM, Fuchs HE, Guaspari A, Bigner DD (1995) Intraarterial administration of melphalan for treatment of intracranial human glioma xenografts in athymic rats. *Cancer Res* 55:3803–3809
1828. Kurtzke JF, Kurland LT (1983) The epidemiology of neurologic diseases. In: Baker AB, Baker LH (eds) *Clinical Neurology*. Harper and Row, Hagerstown, pp 7–14
1829. Kury G, Carter HD (1965) Autoradiographic study of human nervous system tumors. *Arch Pathol* 80:38–42
1830. Kuwahara K, Mori T, Katakura R, Suga T, Suzuki J, Wada T (1984) Follow-up study of 107 germinal tumors and long-term survivors. *Neurol Med Chir (English Abstract)* 24:854–862
1831. Kwa SL, Fine LJ (1980) The association between parental occupation and childhood malignancy. *J Occup Med* 22:792–794
1832. Kyritsis AP, Bondy ML, Xiao M, Berman EL, Cunningham JE, Lee PS, Levin VA, Saya H (1994) Germine p53 gene mutations in subsets of glioma patients. *J Natl Cancer Inst* 86:344–349
1833. Kyuma Y, Kato E, Sekido K et al (1985) Hypothalamic hamartoma successfully treated by operation. Case report. *J Neurosurg* 62:288–290
1834. La Rocca RW, Rosenblum M, Westermarck B, Israel MA (1989) Patterns of proto-oncogene expression in human glioma cell lines. *J Neurosci Res* 24:97–106
1835. Laas E (1935) Ueber die sogenannten Endotheliome der Hirnhäute. *Beitr Pathol Anat* 95:431–442
1836. Labrousse F, Dumas-Duport C, Batorski L, Hoshino T (1991) Histological grading and bromodeoxyuridine labeling index of astrocytomas. *J Neurosurg* 75:202–205
1837. Laerum OD, Rajewsky MF (1975) Neoplastic transformation of fetal rat brain cells in culture after exposure to ethylnitrosourea in vivo. *J Natl Cancer Inst* 55:1177–1187
1838. Laerum OD, Rajewsky MF, Schachner M, Stauron D, Haglid KG, Haugen A (1977) Phenotypic properties of neoplastic cell lines developed from fetal rat brain cells in culture after exposure to ethylnitrosourea in vivo. *Z Krebsforsch Clin Oncol* 82:273–295
1839. Laerum OD, Mork SJ, De Ridder L (1984) The transformation process. *Progr Exp Tumor Res* 27:17–31
1840. Laerum OD, Bjerkvig R, Sverre K et al (1984) Invasiveness of primary brain tumors. *Cancer Metast Rev* 3:223–236
1841. Lagacé R, Delage C, Gagné F (1978) Paraganglioma of the filum terminale. *Can J Neurol Sci* 5:257–260
1842. Lagenaur C, Sommer I, Schachner M (1980) Subclass of astroglia recognized in mouse cerebellum by monoclonal antibodies. *Dev Biol* 79:367–378
1843. Lahl R (1980) Combination of multiple sclerosis and cerebral glioblastoma. *Eur Neurol* 19:192–197
1844. Lai AP, Wierzbicki AS, Norman PM (1991) Immunocytological diagnosis of primary cerebral non-Hodgkin's lymphoma. *J Clin Pathol* 44:251–253
1845. Lakshmi MS, Parker C, Sherbert GV (1993) Metastasis associated mts1 and nm23 genes affect tubulin polymerization in B16 murine melanomas. A possible mechanism of their regulation of metastatic behaviour of tumours. *Anticancer Res* 13:299–304

1846. Lalitha VS, Rubinstein LJ (1979) Reactive glioma in intracranial sarcoma: a form of mixed sarcoma and glioma ("sarcoglioma"). Report of eight cases. *Cancer* 43:246–257
1847. Lam RMY, Golah SA (1979) Atypical fibrous histiocytoma with myxoid stroma. A rare lesion arising from the dura mater of the brain. *Cancer* 43:237–245
1848. Lam RMY, Malik GM, Chason JL (1981) Osteosarcoma of meninges. *Am J Surg Pathol* 5:203–208
1849. Lamb TM, Knecht AK, Smith WC, Stachel SE, Economides AN, Stahl N, Yancopolous GD, Harland RM (1993) Neural induction by the secreted polypeptide noggin. *Science* 262:713–718
1850. Lambert PM (1978) Radiation myelopathy of the thoracic spinal cord in long term survivors treated with radical radiotherapy using conventional fractionation. *Cancer* 41:1751–1760
1851. Lampert PW, Tom MI, Rider WD (1959) Disseminated demyelination of the brain following Co<sup>60</sup> (Gamma) radiation. *Arch Pathol* 68:322–330
1852. Lampert PW, Davis RL (1964) Delayed effects of radiation on the human central nervous system. "Early" and "late" delayed reactions. *Neurology* 14:912–917
1853. Lamperti A, Conger AD, Jenkins O, Cohen G, Rizzo A, Davis ME, Sodicoff M (1988) WR-2721 entry into the brain across a modified blood-brain barriers. *Radiat Res* 115:303–313
1854. Lamproglou I, Chen QM, Boissarie G, Mazon JJ, Poisson M, Baillet F, Leponcin M, Delattre JY (1995) Radiation-induced cognitive dysfunction: an experimental model in the old rat. *Int J Radiat Oncol Biol Phys* 31:65–70
1855. Lana-Peixoto MA, Lagos J, Silbert SW (1977) Primary pigmented carcinoma of the choroid plexus: a light and electron microscopic study. *J Neurosurg* 47:442–450
1856. Landau M (1910) Das diffuse Gliom des Gehirns. *Frankf Z Path* 5:469–514
1857. Landau B, Kwaan H, Verrusio E, Engelhard H, Brem S (1993) Urokinase-type plasminogen activator and plasminogen activator inhibitors in human brain tumors. *Proc Amer Assn Cancer Res* 34:80
1858. Landolt AM (1975) Ultrastructure of human sella tumours. Correlation of clinical findings and morphology. *Acta Neurochir (Wien)* 22:1–167
1859. Lane DP (1993) A death in the life of p53. *Nature* 362:786–787
1860. Lang C, Horn M, Schlote W, Zoellner M, Jacobi G (1992) Desmoplastic (angioblastic) primitive neuroectodermal tumor – a new variant within the PNET spectrum (Abstract). *Clin Neuropathol* 11:268
1861. Lang FF, Miller DC, Koslow M, Newcomb EW (1994) Pathways leading to glioblastoma multiforme: A molecular analysis of genetic alterations in 65 astrocytic tumors. *J Neurosurg* 81:427–436
1862. Lang FF, Miller DC, Pisharody S, Koslow M, Newcomb EW (1994) High frequency of p53 protein accumulation without p53 gene mutation in human juvenile pilocytic, low grade and anaplastic astrocytomas. *Oncogene* 9:949–954
1863. Langford LA, Camel MH (1987) Palisading pattern in cerebral neuroblastoma mimicking the primitive polar spongioblastoma. An ultrastructural study. *Acta Neuropathol (Berl)* 73:153–159
1864. Langmoen IA, Lundar T, Storm-Mathisen I, Lie So, Hovind KH (1991) Management of pediatric pontine gliomas. *Childs Nerv Syst* 7:13–15
1865. Lannering B, Marky I, Nordborg C (1990) Brain tumors in childhood and adolescence in West Sweden, 1970–1984. Epidemiology and survival. *Cancer* 66: 604–609
1866. Lantos PL (1972) The fine structure of the periventricular pleomorphic gliomas induced transplacentally by N-ethylnitrosourea in BD-IX rats. With a note on their origin. *J Neurol Sci* 17:443–460
1867. Lantos PL (1980) Chemical induction of tumors in the nervous system. In: Thomas DGT, Graham DI (eds) *Brain tumors*. Butterworths, London, pp 85–108
1868. Lantos PL, Cox DJ (1976) The origin of experimental brain tumours: a sequential study. *Experientia* 32:1457–1468
1869. Lantos PL, Pilkington GJ (1979) The development of experimental brain tumours: a sequential light and electron microscope study of the subependymal plate. I Early lesions (abnormal cell clusters) *Acta Neuropathol (Berl)* 45:167–175
1870. Laperriere NJ (1990) Critical appraisal of experimental radiation modalities for malignant astrocytomas. *Can J Neurol Sci* 17:199–208

1871. Lapham LW (1962) Cytologic and cytochemical study of neuroglia. I A study of the problem of the mitosis in reactive protoplasmic astrocytes. *Am J Pathol* 41:1-21
1872. Lapras C, Patet JD, Lapras C Jr, Mottolese C (1986) Cerebellar astrocytomas on childhood. *Childs Nerv Syst* 2:55-59
1873. Lapras C, Patet JD, Mottolese C, Gharbi S, Philip T, Mentigny-Brunat M (1987) Treatment of medulloblastomas. Experience with different protocols. *Progr Exp Tumor Res*, 30: 81-90
1874. Lapresle J, Netsky MG, Zimmerman HM (1952) The pathology of meningiomas. A study of 121 cases. *Am J Path* 28:757-791
1875. Laramore GE, Griffin TW, Gerdes AJ, Parker RG (1978) Fast neutron and mixed (neutron-photon) beam teletherapy for grades III and IV astrocytomas. *Cancer* 42:96-103
1876. Laramore GE, Martz KL, Nelson JS, Griffin TW, Chang CH, Horton MD (1989) Radiation Therapy Oncology Group (RTOG) survival data on anaplastic astrocytomas of the brain: does a more aggressive form of treatment adversely impact survivals? *Int J Radiat Oncol Biol Phys* 17:1351-1356
1877. Lassmann H, Jurecka W, Lassmann G, Gebhart W, Matras H, Watzek G (1977) Different types of benign nerve sheath tumors. Light microscopy, electron microscopy and autoradiography. *Virchows Arch (A) Pathol Anat Histol* 375:197-210
1878. Latchaw RE, Hirsch Jr WL (1991) Computerized tomography of intracranial meningiomas. In: Al-Mefty O (ed) *Meningiomas*. Raven, New York, pp 195-207
1879. Latif F, Tory K, Gnarr J, Yao M, Duh F-M, Orcutt ML, Stackhouse T, Kuzmin I, Modi W, Geil L, Glenn G, Choyke P, Walther MM, Weng Y, Duan DSR, Dean M, Glavac D, Richards FM, Crossey PA, Ferguson-Schmitt MA, Le Paslier D, Chumakov I, Cohen D, Chinault AC, Maher ER, Linehan WM, Zbar B, Lerman MI (1993) Identification of the Hippiel-Lindau disease tumor suppressor gene. *Science* 260:1317-1320
1880. Latimer FR, Alsaadi AA, Robbins TO (1987) Cytogenetic studies of human brain tumors and their clinical significance. I Medulloblastoma. *J Neurooncol* 4:287-291
1881. Latov N, Nilaver G, Zimmerman EA, Johnson WG, Silverman AJ, Defendini R, Cofe L (1979) Fibrillary astrocytes proliferate in response to brain injury. *Develop Biol* 72:381-384
1882. Lattes R, Waltner JG (1949) Nonchromaffin paraganglioma of the middle ear (carotid body like tumor; glomus-jugulare tumors). *Cancer* 2:447-468
1883. Lawrence HJ, Largman C (1992) Homeobox genes in normal hematopoiesis and leukemia. *Blood* 80:2445-2453.
1884. Laws ER Jr, Bergstrahl EJ, Taylor WF (1987) Cerebellar astrocytoma in children. *Progr Exp Tumor Res* 30:122-127
1885. Laws ER, O'Connor JS (1970) ATPase in human brain tumors. *J Neurosurg* 33:167-171
1886. Laws ER, Taylor WF, Clifton MB, Okazaki H (1984) Neurosurgical management of low-grade astrocytoma of the cerebral hemispheres. *J Neurosurg* 61:665-673
1887. Lazarides E (1982) Intermediate filaments: a chemically heterogeneous, developmentally regulated class of protein. *Ann Rev Biochem* 51:219-250
1888. Lazebnik YA, Cole S, Cooke CA, Nelson WG, Earnshaw WC (1993) Nuclear events of apoptosis in vitro in cell-free mitotic extracts: a model system for analysis of the active phase of apoptosis. *J Cell Biol* 1:7-22
1889. Le Compte PM (1951) Tumors of the carotid body and related structures (Chemoreceptor system). Atlas of tumor pathology, sect IV, vol 16, AFIP, Washington, DC
1890. Leblanc R, Lozano A, Robitaille Y (1986) Familial mixed oligodendrocytic-astrocytic gliomas. *Neurosurgery* 18:480-482
1891. Lecuire J, Dechaume JP, Bullard P, Bochu M (1971) Les méningiomes de la fosse cérébrale postérieure. *Neurochirurgie* 17:1-146
1892. Lee JP, Wang D-J (1989) Acoustic neurinoma presenting as intratumoral bleeding. *Neurosurgery* 24:764-768
1893. Lee KS, Britton BH, Kelly DLJ (1989) Schwannoma of the facial nerve in the cerebellopontine angle presenting with hearing loss. *Surg Neurol* 31:231-234
1894. Lee MK, Tuttle JB, Rebhun LI, Cleveland DW, Frankfurter A (1990) The expression and post translational modification of a neuron-specific b-tubulin isotype during chick embryogenesis. *Cell Motil Cytoskeleton* 17:118-132
1895. Lee RK, Kishore PRS, Wulfsberg E, Kepes JJ (1978) Supratentorial leptomeningeal heman-gioblastoma. *Neurology* 28:727-730

1896. Lee WH, Bookstein R, Hong F, Young L-J, Shew J-Y, Lee EY-HP (1987) Human retinoblastoma susceptibility gene: cloning, identification and sequence. *Science* 235:1394-1399
1897. Lee WH, Shew JY, Hong FD, Sery TW, Donoso LA, Young LJ, Bookstein R, Lee EY (1987) The retinoblastoma susceptibility gene encodes a nuclear phosphoprotein associated with DNA binding activity. *Nature* 329:642-645
1898. Lee YY, Nauert C, Glass JP (1986) Treatment-related white matter changes in cancer patients. *Cancer* 57:1473-1482
1899. Leedham PW (1972) Primary cerebral rhabdomyosarcoma and the problem of medulloblastoma. *J Neurol Neurosurg Psychiatr* 35:551-559
1900. Leenstra F, Bijlsma EK, Troost D, Oosting J, Westerveld AA, Bosch DA, Hulsebos TJM (1994) Allele loss on chromosomes 10 and 17p and epidermal growth factor receptor gene amplification in human malignant astrocitoma related to prognosis. *Br J Cancer* 70:684-689
1901. Leffingwell SS, Waxweiler RJ, Alexander V, Ludwig HR, Halperin W (1983) Case-control study of gliomas of rat brain among workers employed by a Texas city, Texas chemical plant. *Neuroepidemiology* 2:179-195
1902. Lefkowitz IB, Rorke LB, Packer RJ, Sutton LN, Siegel KR, Katnick R (1987) Atypical teratoid tumor of childhood: definition of an entity. *Ann Neurol* 22:448-449
1903. Lefkowitz IB, Packer RJ, Siegel KR, Sutton LN, Schut L, Evans AE (1990) Results of treatment of children with medulloblastoma/primitive neuroectodermal tumors with lomustine, cisplatin, and vincristine. *Cancer* 65:412-417
1904. Legius E, Marchuck DA, Collins FS, Glover TW (1993) Somatic deletion of the neurofibromatosis 1 gene in a neurofibrosarcoma supports a tumour suppressor gene hypothesis. *Nature Genet* 3:122-126
1905. Légré J, Sedan R, Lavielle J, Clément JP, Paillas JE (1968) Maladie de von Hippel-Lindau. Ablation des angioreticulomes cérébelleux et guérison. Etude neuro-radiologique avec exploration angiographique sélective des localisations viscérales. *Neurochirurgie* 14:583-597
1906. Lehmann J, Krug H (1980) Flow-through fluoro-cytophotometry of different brain tumors. *Acta Neuropathol (Berl)* 48:123-132
1907. Leibel SA, Sheline GE (1987) Radiation therapy for neoplasms of the brain. *J Neurosurg* 66:1-22
1908. Leibel SA, Sheline GE (1991) Tolerance of the brain and spinal cord to conventional irradiation. In: Gutin PH, Leibel SA, Sheline GE (eds) *Radiation injury to the nervous system*. Raven, New York, pp 239-256
1909. Leibel SA, Gutin PH, Warta WM (1989) Survival and quality of life after interstitial implantation of removable high activity iodine-125 sources in the treatment of patients with recurrent malignant gliomas. *Int J Radiat Oncol Biol Phys* 17:1129-1139
1910. Leibowitz U, Yablonski M, Alter M (1971) Tumors of the nervous system. *J Chron Dis* 23:707-714
1911. Leifer D, Moore T, Ukena T, Wilner D, Thor A, Hedley-White ET (1989) Multifocal glioblastoma with liver metastases in the absence of surgery. Case report. *J Neurosurg* 71:772-776
1912. Leith JT, Schilling WA, Wheeler KT (1975) Cellular radiosensitivity of a rat brain tumor. *Cancer* 35:1545-1550
1913. Lekanne Deprez RH, Bianchi AB, Groen NA, Seinzinger BR, Hagemelijer A, van Drunen E, Bootsma D, Koper JW, Avezaat CJJ, Kley N, Zwarthoff EC (1994) Frequent NF2 gene transcript mutations in sporadic meningiomas and vestibular schwannomas. *Am J Hum Genet* 54:1022-1029
1914. LeMay DR, Bucci MN, Farhat SM (1989) Malignant transformation of recurrent meningioma with pulmonary metastases. *Surg Neurol* 31:365-368
1915. Lennert K (1975) Morphology and classification of malignant lymphomas and so-called reticulosarcomas. *Acta Neuropathol (Berl) [Suppl]* VI:1-16
1916. Lennert K (1978) *Malignant lymphomas other than Hodgkin's disease*. Springer, Berlin Heidelberg New York
1917. Lennon VA, Peterson S, Schubert D (1979) Neuroectoderm markers retained in phenotypical skeletal muscle cells arising from a glial cell line. *Nature* 281:586-588
1918. Leonhardt H (1966) Über ependymale Tanycyten des III. Ventrikels beim Kaninchen in elektronenmikroskopischer Betrachtung. *Z Zellforsch* 74:1-11

1919. Lerman RI, Kaplan ES, Daman L (1972) Ganglioneuroma-paraganglioma of the intradural filum terminale. Case report. *J Neurosurg* 36:652-658
1920. LeRoux P, Hope A, Lofton S, Harris AB (1989) Lipomatous meningioma. An uncommon tumor with distinct radiographic findings. *Surg Neurol* 32:360-365
1921. Lesch KP, Gross S (1987) Estrogen receptor immunoreactivity in meningiomas. Comparison with the finding activity of estrogen, progesterone, and androgen receptors. *J Neurosurg* 67:237-243
1922. Lesch KP, Gross S (1987) Androgen receptor finding activity in meningiomas. *Surg Neurol* 28:176-180
1923. Lesnick JE, Chayt KJ, Bruce DA, Rorke LB, Trojanowski J, Savino PJ, Schatz NJ (1985) Familial pineoblastoma. Report of two cases. *J Neurosurg* 62:930-932
1924. Letendre L, Banks PM, Reese DE, Miller RM, Scanlon PW, Kiely JM (1982) Primary lymphoma of the central nervous system. *Cancer* 49:939-943
1925. Levi F, La Vecchia C, Te Van-Cong (1990) Descriptive epidemiology of malignant brain tumours in the Swiss Canton of Vaud. *Neuroepidemiology* 9:135-142
1926. Levin B (1985) Chemotherapy of primary brain tumors. *Neurol Clin* 3:855-866
1927. Levin BA, Edwards MS, Byrd A (1979) Quantitative observations of the acute effects of X-irradiation on brain capillary permeability, part I. *Int J Radiat Oncol Biol Phys* 5:1627-1631
1928. Levin V, Freeman M, Landahl H (1975) The permeability characteristic of brain adjacent to intracerebral rat tumors. *Arch Neurol* 32:785-791
1929. Levin VA, Silver P, Hannigan J, Wilson CB (1990) Superiority of postradiotherapy adjuvant chemotherapy with CCNU, procarbazine and vincristine (PCV) over BCNU for anaplastic gliomas: NCOG 6G61 final report. *Int J Radiat Oncol Biol Phys* 18:321-324
1930. Levin VA, Prados MR, Wara WM, Davis RL, Gutin PH, Phillips TL, Lamborn K, Wilson CB (1995) Radiation therapy and bromodeoxyuridine chemotherapy followed by procarbazine, lomustine, and vincristine for the treatment of anaplastic gliomas. *Int J Radiat Oncol Biol Phys* 32:75-83
1931. Levine AJ (1993) The tumor suppressor genes. *Ann Rev Biochem* 62:623-651
1932. Levine AJ, Momand J, Finlay CA (1991) The p53 tumor suppressor gene. *Nature* 351:453-456
1933. Levine J, Card P (1987) Light and electron microscopic localization of cell surface antigen (NG2) in the rat cerebellum: association with smooth protoplasmic astrocytes. *J Neurosci* 7:2711-2720
1934. Levison SW, Chuang C, Abramson B, Goldman E (1993) The migrational patterns and developmental fates of glial precursors in the rat subventricular zone are temporally regulated. *Development* 119:611-627
1935. Leviton A (1984) Principles of epidemiology. In: Cohen ME, Duffner PK (eds) *Brain tumors in children. Principles of diagnosis and treatment*. Raven, New York, pp 22-46
1936. Leviton A, Fulcher A, Gilles F (1978) Survival status of children with cerebellar gliomas. *J Neurosurg* 48:29-33
1937. Levitt EJ, Dawson DM, Rosenthal DS, Moloney WC (1980) CNS involvement in the non-Hodgkin's lymphomas. *Cancer* 45:545-552
1938. Levitt P, Rakic P (1980) Immunoperoxidase localization of glial fibrillary acidic protein in radial glial cells and astrocytes of the developing Rhesus monkey brain. *J Comp Neurol* 193:815-840
1939. Levitt P, Cooper MI, Rakic P (1981) Coexistence of neuronal and glial precursor cells in the cerebral ventricular zone of fetal monkey: an ultrastructural immunoperoxidase analysis. *J Neurosci* 1:27-39
1940. Levy LF, Elvidge AR (1956) Astrocytoma of the brain and spinal cord. A review of 176 cases, 1940-1949. *J Neurosurg* 13:413-443
1941. Levy RM, Bredsen DE, Rosenblum ML (1985) Neurological manifestation of the acquired immunodeficiency syndrome (AIDS): experience at UCSF and review of the literature. *J Neurosurg* 62:475-495
1942. Lewis P (1967) Carcinoma of the choroid plexus. *Brain* 90:177-186
1943. Lewis P (1968) The fate of the subependymal cell in the adult rat brain, with a note on the origin of microglia. *Brain* 91:721-736
1944. Lewis P (1981) Cell proliferation in the postnatal nervous system and its relationship to the origin of gliomas. *Semin Neurol* 1:181-187

1945. Lewis PD, Fülöp Z, Hajós E, Balázs R, Woodhams PL (1977) Neuroglia in the internal granular layer of the developing rat cerebellar cortex. *Neuropathol Appl Neurobiol* 3:183–190
1946. Ley A, Campillo D, Oliveras C (1961) Extracranial metastasis of glioblastoma multiforme. *J Neurosurg* 18:313–330
1947. Lhermitte J, Duclos P (1920) Sur un ganglioneurome diffus du cortex du cervelet. *Bull Assoc Fr Cancer* 9:99–106
1948. Li H, Hamou MF, de Tribolet N, Jaufeerally R, Hofmann M, Diserens AC, Van Meir EG (1993) Variant CD44 adhesion molecules are expressed in human brain metastases but not in glioblastomas. *Cancer Res* 53:5345–5349
1949. Li Y, Bollag G, Clark R, Stevens J, Conroy L, Fults D, Ward K, Friedman E, Samowitz W, Robertson M, White R, Cawthon R (1992) Somatic mutations in the neurofibromatosis 1 gene in human tumors. *Cell* 69:275–281
1950. Li Y, O'Connell P, Breidenbach HH, Cawthon R, Stevens J, Xu G, Neil S, Robertson M, White R, Viskochil D, (1995) Genomic organization of the Neurofibromatosis 1 gene (NF1). *Genomics* 25:9–18
1951. Liao SK, Clarke BJ, Kwong PO, Brickenden A, Gallie BL, Dant PB (1981) Common neuroectodermal antigens on human melanoma, neuroblastoma, retinoblastoma, glioblastoma and fetal brain revealed by hybridoma antibodies raised against melanoma cells. *Eur J Immunol* 11:450–454
1952. Liao SY, Choi BH (1986) Expression of glial fibrillary acidic protein by neoplastic cells of müllerian origin. *Virchows Arch B* 52:185–191
1953. Liber AF, Lisa JR (1937) Rosenthal fibres in non-neoplastic syringomyelia. *J Nerv Ment Dis* 86:549–555
1954. Libermann TA, Nusbaum HR, Razon N, Kris R, Lax I, Soreq H, Whittle N, Waterfield MD, Ullrich A, Schlessinger JH (1985) Amplification, enhanced expression and possible rearrangement of EGF receptor gene in primary human brain tumors of glial origin. *Nature* 313:144–147
1955. Lichtenstein BW (1971) Hamartomas and phacomatoses. In: Minckler J (ed) *Pathology of the nervous system vol 2*. McGraw-Hill, New York pp 1897–1905
1956. Lichtenstein L (1952) *Bone tumors*. Mosby, St Louis
1957. Lichtor T, Dohrmann GJ (1986) Respiratory patterns in human brain tumors. *Neurosurgery* 19:896–899
1958. Liebaltd G, Descalzo C (1963) Idiopathische (nicht-arteriosklerotische) Verkalkungsvorgänge im Zentralnervensystem. *Dtsch Z Nervenheilkd* 184:388–426
1959. Liliequist B, Thulin C-A, Tovi D, Wiberg A, Öhman J (1972) Neurinoma of the labyrinthine portion of the facial nerve. Case report. *J Neurosurg* 37:105–109
1960. Lilja A, Bergstrom K, Spannare B (1981) Reliability of computed tomography in assessing histopathological features of malignant supratentorial gliomas. *J Comput Assist Tomogr* 5:625–636
1961. Lim R, Mitsonobu K (1974) Brain cells in culture: morphological transformation by a protein. *Science* 185:63–66
1962. Limas C, Tio FO (1972) Meningeal melanocytoma (“melanotic meningioma”). Its melanocytic origin as revealed by electron microscopy. *Cancer* 30:1286–1294
1963. Lin RS, Dishinger PC, Conde J (1985) Occupational exposure to electromagnetic fields and the occurrence of brain tumors. *J Occup Med* 27:413–419
1964. Lin SR, Bryson MM, Gobien R, Fitz CR, Lee Y-Y (1978) Neuroradiologic study of hamartomas of the tuber cinereum and hypothalamus. *Neuroradiology* 16:17–19
1965. Lin SS, Johnson PC, Sonntag VKH (1989) Meningiomatosis: a report of six cases with special reference to the occurrence of neurofibrillary tangles. *J Neuropathol Exp Neurol* 45:426–446
1966. Lindau A (1926) Studien über Kleinhirncysten. Bau, Pathogenese und Beziehungen zur Angiomatosis retinae. *Acta Pathol Microbiol Scand [Suppl]* 1
1967. Lindboe ChF, Cappelm J, Kepes JJ (1992) Pleomorphic xanthoastrocytoma as a component of a cerebellar ganglioma: cases report. *Neurosurgery* 31:353–355
1968. Lindegaard K-F, Mork SJ, Eide GE, Halvorsen TB, Hatlevoll R, Solgaard T, Dahl O, Ganz J (1987) Statistical analysis of clinicopathological features, radiotherapy, and survival in 170 cases of oligodendroglioma. *J Neurosurg* 67:224–230



1969. Lindley JG, Challa VR, Kelly Jr DL (1991) Meningiomas and brain edema. In: Al-Mefty O (ed) *Meningiomas*. Raven, New York, 59–73
1970. Linfoot PA, Barcellos-Hoff MH, Brent TP, Marton LJ, Deen DF (1988) Cell-cycle phase specific killing by 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) in sensitive and resistant cells. *NCI Monogr Ser* 6:183–186
1971. Linskey ME, Gilbert MR (1995) Glial differentiation: a review with implications for new directions in neuro-oncology. *Neurosurgery* 36:11–21
1972. Linstadt DE, Edwards MSB, Prados M, Larson DA, Wara WM (1991) Hyperfractionated irradiation for adults with brainstem gliomas. *Int J Radiation Oncol Biol Phys* 20:757–760
1973. Liotta LA (1982) Tumor extracellular matrix. *Lab Invest* 47:112–113
1974. Liotta LA (1986) Tumor invasion and metastases-role of the extracellular matrix: Rhoads Memorial Award Lecture. *Cancer Res* 46:1–7
1975. Lipinski M, Braham K, Caillard J-M, Carlu C, Tursr T (1983) The HNK-1 antibody detects an antigen expressed on neuroectodermal cells. *J Exp Med* 158:1773–1780
1976. Lipper S, Dalzell JC, Watkins PJ (1979) Ultrastructure of psammoma bodies in meningioma in tissue culture. *Arch Pathol Lab Med* 103:670–675
1977. Lippitz BE, Halperin E, Griffith OW, Colvin OM, Honore G, Ostertag CB, Bigner DD, Friedman HS (1990) L-buthionine-sulfoximine-mediated radiosensitization in experimental interstitial radiotherapy of intracerebral D-54 MG glioma xenografts in athymic mice. *Neurosurgery* 26:255–261
1978. Lipsmeyer EA (1972) Development of malignant cerebral lymphoma in a patient with systemic lupus erythematosus treated with immunosuppression. *Arthritis Rheum* 15:183–186
1979. Lipson A, Bale P (1985) Ependymoblastoma associated with prenatal exposure to diphenylhydantoin and methylphenobarbitone. *Cancer* 55:1859–1862
1980. List CF, Dowman CE, Bagchi BK, Bebin J (1958) Posterior hypothalamic hamartomas and gangliogliomas causing precocious puberty. *Neurology* 8:164–174
1981. Liszczak T, Richardson EP, Phillips JP, Jacobson S, Kornblith PL (1978) Morphological, biochemical, ultrastructural, tissue culture and clinical observations of typical and aggressive craniopharyngiomas. *Acta Neuropathol (Berl)* 43:191–203
1982. Lithicum FH, Brackman DE (1980) Bilateral acoustic tumors. A diagnostic and surgical challenge. *Arch Otolaryngol* 106:729–734
1983. Litowski NS, Hinton D, Raffel C (1994) The lack of a role for p53 in astrocytomas in pediatric patients. *Neurosurgery* 34:967–972
1984. Little JR, Dale AJD, Okazaki H (1974) Meningeal carcinomatosis: clinical manifestations. *Arch Neurol* 30:138–143
1985. Littman P, Wang CC (1975) Reticulum cell sarcoma of the brain. A review of the literature and a study of 19 cases. *Cancer* 35:1412–1420
1986. Littman P, Jarrett P, Bilaniuk LT, Rorke LB, Zimmerman R, Bruce D, Carabell S, Schut L (1980) Pediatric brain stem gliomas. *Cancer* 45:2787–2792
1987. Liu HM, Boogs J, Kidd J (1976). Ependymomas of childhood. I Histological survey and clinicopathological correlation. *Childs Brain* 2:92–110
1988. Liu JP, Baker J, Perkins AS, Robertson EJ, Efstratiadis A (1993) Mice carrying null mutations of the genes encoding insulin-like growth factor (Igf-1) and type I IGF receptor (Igf1r). *Cell* 75:59–72
1989. Livingstone LR, White A, Sprouse J, Livanos E, Jacks T, Tlsty TD (1992) Altered cell cycle arrest and gene amplification potential accompany loss of wild-type p53. *Cell* 70:923–935
1990. Liwnicz BH, Rubinstein LJ (1979) The pathways of extraneural spread in metastasizing gliomas: a report of three cases and critical review of the literature. *Hum Pathol* 10:453–467
1991. Liwnicz BH, Berger TS, Liwnicz BS, Aron BS (1985) Radiation-associated glioblastomas: a report of four cases and analysis of post-irradiation tumors of the central nervous system. *Neurosurgery* 17:436–445
1992. Llena JF, Céspedes G, Hirano A, Zimmerman HM (1976) Vascular alterations in delayed radiation necrosis of the brain. *Arch Pathol Lab Med* 100:531–534
1993. Llena JF, Wisoff HS, Hirano A (1982) Gangliocytic paraganglioma in the cauda equina region with biochemical and neuropathological studies. *J Neurosurg* 56:280–282

1994. Lloyd RV, Warner TF (1984) Immunohistochemistry of neuron-specific enolase. In De Lellis RA (ed) *Advances in immunohistochemistry*. Masson, New York pp 127–140
1995. Lloyd R, Sisson JC, Shapiro B, Verhofstad AAJ (1986) Immunohistochemical localization of epinephrine, norepinephrine, catecholamine synthesizing enzymes, and chromogranin in neuroendocrine cells and tumors. *Am J Pathol* 125:45–54
1996. Lobato RD, Sarabia M, Castro S, Esparza J, Cordobes F, Portillo J, Rivas JJ (1986) Symptomatic subependymoma: report of four new cases studied with computed tomography and review of the literature. *Neurosurgery* 19:594–598
1997. Locatelli D, Bottoni A, Uggetti C, Gozzoli L (1987) Multiple meningiomas evaluated by computed tomography. *Neurochirurgia* 30:8–10
1998. Locksmith JP, Powers WE (1968) Permanent radiation myelopathy. *Am J Roentgenol Radium Ther Nucl Med* 102:916–926
1999. Locoge M (1958) Considération sur la pathogénie des épidermo-dermoïdes et tératomes du système nerveux. *Acta Neurol Psychiatr Belg* 58:753–757
2000. Loddin P, Kindblom LG, Angervall L, Stenman G (1990) Cellular Schwannoma. A clinico-pathologic study of 29 cases. *Virch Arch (A)* 416:237–248
2001. Loeffler JS, Ervin TJ, Manch P, Skarin A, Weinstein HJ, Canellos G, Cassady R (1985) Primary lymphomas of the central nervous system: patterns of failure and factors that influence survival. *J Clin Oncol* 3:490–494
2002. Loeffler JS, Shrieve DC, Alexander E (1994) Radiosurgery for glioblastoma multiforme: the importance of selection criteria. *Int J Radiat Oncol Biol Phys* 30:3 731–746
2003. Löfgren F (1970) The infundibular recess, a component in the hypothalamo-adenohypophyseal system. *Acta Morph Neerl Scand* 3:55–78
2004. Loftus CM, Copeland BR, Carmel PW (1985) Cystic supratentorial gliomas: natural history and evaluation of modes of surgical therapy. *Neurosurgery* 17:19–24
2005. Lolait SJ, Underwood JR, Mu FT, Alderuccio F, Dow CA, Pedersen TS, Chalmers PJ, Toh BH (1984) Vimentin intermediate filaments in cultures of human meningiomas. *Neuropathol Appl Neurobiol* 10:321–331
2006. Lona C, Tabiaddon G, Dossi Currò B, Mohsenipour I (1988) Incidence of primary intracranial tumors in the Province of Bolzano, 1980–1984. *Ital J Neurol Sci* 9:237–241
2007. Long DM (1970) Capillary ultrastructure and the blood-brain barrier in human malignant brain tumors. *J Neurosurg* 32:127–144
2008. Lopez DA, Silvers DN, Hellwig EB (1974) Cutaneous meningiomas – a clinicopathologic study. *Cancer* 34:728–744
2009. Lorentzen M, Hägerstrand I (1980) Congenital ependymoblastoma. *Acta Neuropathol (Berl)* 49:71–74
2010. Los M, Van de Craen M, O'Penning LC, Schenk H, Westendorp M, Bauerle PA, Droge W, Krammer PH, Flers W, Schulze-Osthoff K (1995) Requirement of an ICE/CED-3 protease for Fas/APO.1-mediated apoptosis. *Nature* 375:81–83
2011. Lossignol D, Grossman SA, Sheidler VR, Griffin CA, Piantadosi S (1990) Familial clustering of malignant astrocytomas. *J Neurooncol* 9:139–145
2012. Louis DN (1994) The p53 gene and protein in human brain tumors. *J Neuropathol Exp Neurol* 53:11–21
2013. Louis DN, Gusella JF (1995) A tiger behind many doors: multiple genetic pathways to malignant glioma. *TIG* 11:412–415
2014. Louis DN, von Deimling A (1995) Hereditary tumor syndromes of the nervous system: overview and rare syndromes. *Brain Pathol* 5:145–151
2015. Louis DN, Hedley-White ET, Martuza RL (1990) Sarcomatous proliferation of the vasculature in a subependymoma: a follow-up study of sarcomatous dedifferentiation. *Acta Neuropathol (Berl)* 80:573–574
2016. Louis DN, Swearingen B, Linggood RM, Dickersin GR, Kretschmar C, Bhan AK, Hedley-White T (1990) Central nervous system neurocytoma and neuroblastoma in adults – report of eight cases. *J Neurooncol* 9:231–238
2017. Louis DN, Edgerton S, Thor AD, Hedley-White ET (1991) Proliferating cell nuclear antigen and Ki-67 immunohistochemistry in brain tumors: a comparative study. *Acta Neuropathol (Berl)* 81:675–679

2018. Louis DN, Mehan SM, Ferrante RJ, Hedley-White T (1992). Use of the silver molecular organizer region (Ag NOR) technique in the differential diagnosis of central nervous system neoplasia. *J Neuropathol Exp Neurol* 51:150–157
2019. Louis DN, von Deimling A, Dickersin GR, Dooling EC, Seizinger BR (1992) Desmoplastic cerebral astrocytomas of infancy: a histopathologic, immunohistochemical, ultrastructural, and molecular genetic study. *Hum Pathol* 23:1402–1409
2020. Louis DN, von Deimling A, Chung RY, Rubio MP, Whaley JM, Eibl RH, Ohgaki H, Wiestler OD, Thor AD, Seizinger BR (1993) Comparative study of p53 gene and protein alterations in human astrocytic tumors. *J Neuropathol Exp Neurol* 52:31–38
2021. Louis DN, Rubio MP, Correa KM, Gusella JF, von Deimling A (1993) Molecular genetics of pediatric brain stem gliomas. Application of PCR techniques to small and archival brain tumor specimens. *J Neuropathol Exp Neurol* 52:507–515
2022. Louis DN, Ramesh V, Gusella JF (1995) Neuropathology and molecular genetics of neurofibromatosis 2 and related tumors. *Brain Pathol* 5:163–172
2023. Louis M (1774) Mémoires sur les tumeurs fongueuses de la dure-mère. *Mém Acad Roy Chir* 5:1–19
2024. Lovaste MG, Ferrari G, Rossi G (1986) Epidemiology of primary intracranial neoplasms. Experiment in the province of Trento (Italy), 1977–1984. *Neuroepidemiology* 5:220–232
2025. Love JG, Kernohan JW (1936) Dermoids and epidermoidal tumors of the CNS. *JAMA* 107:1876–1882
2026. Lowe J, Morrell K, Lennox G, Landon M, Mayer RJ (1989) Rosenthal fibres are based on the ubiquitination of glial filaments. *Neuropathol Appl Neurobiol* 15:45–53
2027. Lowe SW, Schmitt EM, Smith SW, Osborne BA, Jacks T (1993) p53 is required for radiation-induced apoptosis in mouse thymocytes. *Nature* 362:847–849
2028. Lowe WL Jr, Mayer T, Karpen CW, Lorentzen LR (1992) Regulation of insulin-like growth factor I production in rat C6 glioma cells: possible role as an autocrine/paracrine growth factor. *Endocrinology* 130:2683–2691
2029. Lowry OH, Berger SJ, Chi MM-Y, Carter G, Blackshaw A, Outlaw W (1977) Diversity of metabolic patterns in human brain tumors. I. High energy phosphate compounds and basic composition. *J Neurochem* 29:959–977
2030. Lowry OH, Berger SJ, Carter JG, Chi MM-Y, Manchester JK, Knor J, Pusateri ME (1983) Diversity of metabolic patterns in human brain tumors: enzymes of energy metabolism and related metabolites and cofactors. *J Neurochem* 41:994–1010
2031. Lozano R, Costero I (1926) Ein Tumor des Verlängerten Rückenmarks. *Dtsch Ztschr Chir* 198:270–276
2032. Lu S, Bogarad LD, Murtha MT, Ruddle FH (1992) Expression pattern of a murine homeobox gene, Dbx, displays extreme spatial restriction in embryonic forebrain and spinal cord. *Proc Natl Acad Sci USA* 89:8053–8057
2033. Lübke J, von Ammon K, Watanabe K, Hegi ME, Kleihus P (1995) Familial brain tumor syndrome associated with a p53 germline deletion of codon 236. *Brain Pathol* 5:15–23
2034. Luccarelli G (1980) Glioblastoma multiforme of the cerebellum. Description of 3 cases. *Acta Neurochir (Wien)* 53:107–116
2035. Ludlow J, DeCaprio J, Huang C, Lee W-H, Paucha E, Livingston D (1989) SV40 large T antigen binds preferentially to an underphosphorylated member of the retinoblastoma susceptibility gene product family. *Cell* 56:57–65
2036. Ludwig CL, Smith MT, Godfrey AD, Armbrustmacher VW (1986) A clinicopathological study of 323 patients with oligodendrogliomas. *Ann Neurol* 19:15–21
2037. Ludwin SK (1984) Proliferation of mature oligodendrocytes after trauma to the central nervous system. *Nature* 308:274–275
2038. Ludwin SK (1985) Reaction of oligodendrocytes and astrocytes to trauma and implantation. *Lab Invest* 52:20–30
2039. Ludwin SK, Rubinstein LJ, Russell DS (1975) Papillary meningioma: a malignant variant of meningioma. *Cancer* 36:1363–1373
2040. Ludwin SK, Kosek JC, Eng LF (1976) The topographical distribution of S-100 and GFAP proteins in the adult rat brain; an immunohistochemical study using horseradish peroxidase-labeled antibodies. *J Comp Neurol* 165:197–208

2041. Luevano-Flores E, Sotelo J, Tena-Suck M (1985) Glial polyp (glioma) of the uterine cervix. Report of a case with demonstration of glial fibrillary acidic protein. *Gynecol Oncol* 21:385–392
2042. Lukes RJ, Collins RD (1975) New approaches to the classification of the lymphomata. *Br J Cancer [Suppl II]* 31:1–28
2043. Lumsden CE (1959) Tissue culture in relation to tumours of the nervous system. In: Russell D, Rubinstein LJ (eds) *Pathology of tumours of the nervous system*, 1st edn. Arnold, London, p 272
2044. Lumsden CE (1970) The neuropathology of multiple sclerosis. In: Vinken PJ, Bruyn GW (eds) *Handbook of clinical neurology* vol 9. North Holland, Amsterdam, pp 217–309
2045. Lumsden CE (1971) The study by tissue culture of tumours of the nervous system. In: Russell DS, Rubinstein LJ (eds) *Pathology of tumours of the nervous system*, 2nd edn. Arnold, London
2046. Lunardi P, Missori P, Gagliardi FM, Fortuna A (1989) Long term results of the surgical treatment of spinal dermoids and epidermoid tumors. *Neurosurgery* 25:860–864
2047. Luse SA (1956) Electron microscopic observations of the central nervous system. *J Biophys Biochem Cytol* 2:513–518
2048. Luse SA (1960) Electron microscopic studies of brain tumors. *Neurology* 10:881–905
2049. Luse SA (1961) Ultrastructural characteristics of normal and neoplastic cells. *Progr Exp Tumor Res* 2:1–35
2050. Luse SA, Kernohan JW (1955) Squamous cell nests of the anterior pituitary gland. *Cancer* 8:623–628
2051. Lusins JO, Nakagawa H (1981) Multiple meningiomas evaluated by computed tomography. *Neurosurgery* 9:137–141
2052. Luthert PS, Lantos PL (1985) A morphometric study of the microvasculature of rat glioma. *Neuropathol Appl Neurobiol* 11:461–473
2053. Luyendijk W (1959) Calcification of a parasagittal meningeoma. *Folia Psychiatr Neerl* 52:472–475
2054. Luyendijk W, Staal A (1964) On a brain ependymoma in a two month old infant. *Zbl Neurochir* 24:100–102
2055. Lye RH, Elstow SF, Weiss JB (1986) Neovascularization of intracranial tumors. In: Walker MD, Thomas DGT (eds) *Biology of brain tumors*. Nijhoff, Boston, pp 61–74
2056. Lynn JA, Panopio IT, Martin JH, Shaw ML, Race GJ (1968) Ultrastructural evidence of astroglial histogenesis of the monstrocellular astrocytoma (so-called monstrocellular sarcoma of brain). *Cancer* 22:356–366
2057. Maat-Schieman ML, Bots GT, Thomeer RT (1985) Malignant astrocytoma following radiotherapy for craniopharyngioma. *Br J Radiol* 58:480–482
2058. Mabon RF, Svien HJ, Adson AW, Kernohan JW (1950) Astrocytomas of the cerebellum. *Arch Neur Psych* 64:74–88
2059. Macdonald DR, Gaspar LE, Cairncross JG (1990) Successful chemotherapy for newly diagnosed aggressive oligodendroglioma. *Ann Neurol* 27:573–574
2060. Machacek F (1966) Lipom des Balkens und symmetrische Plexuslipome. *Wien Klin Wschr* 78:390–393
2061. Mack EE, Wilson CB (1993) Meningiomas induced by high-dose cranial irradiation. *J Neurosurg* 79:28–31
2062. Mackintosh FR, Colby TV, Podolsky WJ, Burke JS, Hoppe RT, Rosenfeldt FP, Rosemberg SA, Kaplan HS (1982) Central nervous system involvement in non-Hodgkin's lymphomas: an analysis of 105 cases. *Cancer* 49:586–595
2063. MacMahon E, Glass J, Hayward S, Mann R, Becker P, Charache P, McArthur J, Ambinder R (1991) Epstein-Barr virus in AIDS-related primary central nervous system lymphoma. *Lancet* 338:969–973
2064. Madsen C, Schroder H (1994) Stereological analysis of nuclear volume in recurrent meningiomas. *J Neuropathol Exp Neurol* 53:272–275
2065. Magee PN, Barnes JN (1956) The production of malignant primary hepatic tumours in the rat by feeding dimethylnitrosoamine. *Br J Cancer* 10:114–120
2066. Magini G (1988) Sur la neuroglie et les cellules nerveuses cérébrales chez les foetus. *Arch Ital Biol* 9:59–60

2067. Mahaley MS, Day ED, Bigner D (1969) Problem inherent to the in vivo localization of anti-brain tumor antibodies. *Ann NY Acad Sci* 159:451-460
2068. Mahaley MS, Mahaley JL, Day ED (1965) The localization of radioantibodies in human brain tumors. II Radioautography. *Cancer Res* 25:779-793
2069. Mahaley MS Jr, Brooks WH, Roszman TL, Bigner DD, Dudka L, Richardson S (1977) Immunobiology of primary intracranial tumours. Part I Studies of the cellular and tumoral general immune competence of brain-tumor patients. *J Neurosurg* 46:467-476
2070. Mahaley MS Jr, Whaley RA, Blue M, Bertsch L (1986) Central neurotoxicity following intracarotid BCNU chemotherapy for malignant gliomas. *J Neurooncol* 3:297-314
2071. Mahaley MS, Mettlin C, Natazajan N, Laws ER, Peace B (1989) National survey of patterns of care for brain brain tumors patients. *J Neurosurg* 71:826-836
2072. Mahmood A, Caccamo DV, Tomecek FJ, Malik GM (1993) Atypical and malignant meningiomas: a clinicopathological review. *Neurosurgery* 33:955-963
2073. Mahoney W (1936) Die Epidermoide des Zentralnervensystems. *Z Gesamte Neurol Psychiatr* 155:416-471
2074. Maidment SL, Rooprai HK, Rucklidge G, Pilkington GJ (1994) Metalloproteinases secretion by human brain tumours in vitro. *Neuropathol Appl Neurobiol* 20:303
2075. Maier H, Morimura T, Ofner D, Hallbrucker C, Kitz K, Budka H (1990) Argyrophilic nucleolar organizer region proteins (AgNORs) in human brain tumors: Relations with grade of malignancy and proliferation indices. *Acta Neuropathol (Berl)* 80:156-162
2076. Maiorano E, Maiorano G (1985) Xantoastrocitoma pleomorfo: aspetti istologici ed immunostochimici e revisione della letteratura. *Riv Anat Pat Oncol* 44:265-276
2077. Majlessi H, Shariat AS, Katirai A (1978) Nasopharyngeal craniopharyngioma. Case report. *J Neurosurg* 49:119-120
2078. Malaise EP, Fertil B, Chavaudra N, Guichard M (1986) Distribution of radiation sensitivities for human tumor cells of specific histological types: comparison of in vitro to in vivo data. *Int J Radiation Oncol Biol Phys* 12:617-624
2079. Malden LT, Novak U, Kay AH, Burgess AW (1988) Selective amplification of the cytoplasmic domain of the epidermal growth factor receptor gene in glioblastoma multiforme. *Cancer Res* 48:2711-2714
2080. Maleki M, Robitaille J, Bertrand G (1983) Atypical xanthoastrocytoma presenting as a meningioma. *Surg Neurol* 20:235-238
2081. Malkin D, Li FP, Strong LC, Fraumeni JF, Nelson C, Kim DH, Kassel J, Gryka MA, Bishoff FZ, Taisky MA, Friend SH (1990) Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. *Science* 250:1221-1228
2082. Mallory FB (1902) Three gliomata of ependymal origin: two in the fourth ventricle, one subcutaneous over the coccyx. *J Med Res* 8:1-13
2083. Mallory FB (1920) The type cell of the so-called dural endothelioma. *J Med Res* 41:349-364
2084. Mamelak AN, Prados MD, Obana WG, Cogen PH, Edwards MSB (1994) Treatment options and prognosis for multicentric juvenile pilocytic astrocytoma. *J Neurosurg* 81:24-30
2085. Manaka S, Teramoto A, Takakura K (1985) The efficacy of radiotherapy for craniopharyngioma. *J Neurosurg* 62:648-656
2086. Mancardi GL, De Martini I, Cadoni A, Zicca A, Schenone A, Bionchini D, Zaccheo D (1989) Immunocytochemical studies of human Schwann cells show properties similar to astrocytes. *Clin Neuropathol* 7:185
2087. Mancini J, Simonin G, Chabrol B (1991) Signes initiaux. In: Choux M, Lena G, Genitori L (eds) *Le craniopharyngiome de l'enfant*. *Neurochir (Paris)* [Suppl 1]: 31-43
2088. Mancuso TF (1982) Epidemiological study of tumors of the central nervous system in Ohio. *Ann NY Acad Sci* 381:17-39
2089. Mancuso TF, Ciocco A, El-Attar AA (1968) An epidemiological approach to the rubber industry: a study based on departmental experience. *J Occup Med* 10:213-232
2090. Mandybur TI, Gore I (1969) Amyloid in late postirradiation necrosis of brain. *Neurology* 19:983-992
2091. Manelfe C, Lasjannias P, Ruscelleda J (1986) Preoperative embolization of intracranial meningiomas. *AJNR* 7:963-972

2092. Mangiardi JR, Yodice P (1990) Metabolism of malignant astrocytoma. *Neurosurgery* 26:1–19
2093. Mann J, Yates PC, Ainslie JP (1953) Unusual case of double orbital tumour. *Br J Ophthalmol* 37:758–762
2094. Manno NJ, Uihlein A, Kernohan JW (1962) Intraspinal epidermoids. *J Neurosurg* 19:754–765
2095. Mannoji H, Becker LE (1988) Ependymal and choroid plexus tumors. Cytokeratin and GFAP expression. *Cancer* 61:1377–1385
2096. Mannoji H, Takeshita I, Fukui M, Ohta M, Kitamura K (1981) Glial fibrillary acidic protein in medulloblastoma. *Acta Neuropathol (Berl)* 55:63–69
2097. Mansuy L, Allegre G, Courjon J, Tomasi M, Thierry A (1967) Analyse d'une série opératoire de 49 oligodendrogliomes. Avec 3 localisations infra-tentorielles. *Neurochirurgie (Paris)* 13:679–700
2098. Mantravadi RVP, Phatak R, Bellur S, Lieber EJ, Haas R (1982) Brain-stem gliomas: an autopsy study of 25 cases. *Cancer* 49:1294–1296
2099. Manuelidis EE (1972) Glioma in trauma. In: Minckler J (ed) *Pathology of the nervous system*, vol 2. McGraw-Hill, New York, pp 2237–2240
2100. Manuelidis EE, Solitaire G (1971) Glioblastoma multiforme. In: J Minckler (ed) *Pathology of the Nervous System*, vol 2. McGraw-Hill, New York, pp 2026–2071
2101. Manz HJ, Woolley PV, Ornitz RD (1979) Delayed radiation necrosis of brainstem related to fast neutron beam irradiation. Case report and literature review. *Cancer* 33:473–479
2102. Marangos PJ, Zis AP, Clark RL, Goodwin FK (1978) Neuronal, and non-neuronal and hybrid forms of enolase in brain: structural, immunological and functional comparisons. *Brain Res* 150:117–133
2103. Maranzano E, Latini P (1995) Effectiveness of radiation therapy without surgery in metastatic spinal cord compression: Final results from a prospective trial. *Int J Radiat Oncol Biol Phys* 32:959–967
2104. Maraziotis T, Perentes E, Karamitopoulou E, Nakagawa Y, Gessaga EC, Probst A, Frankfurter A (1992) Neuron-associated class III b-tubulin isotype, retinal S-antigen, synaptophysin and glial fibrillary acidic protein in human medulloblastomas. A clinicopathological analysis of 36 cases. *Acta Neuropathol (Berl)* 84:355–363
2105. Marchese MJ, Zaider M, Hall EJ (1987) Dose rate effects in normal and malignant cells of human origin. *Br J Radiol* 60:573–576
2106. Marchuk DA, Saulino AM, Tavakkol R, Swaroop M, Wallace MR, Andersen LB, Mitchell AL, Gutman DH, Boguski M, Collins FS (1991) cDNA cloning of the type 1 neurofibromatosis gene: complete sequence of the NF-1 gene product. *Genomics* 11:931–940
2107. Marelle L, Raphael M, Henin D, Vazeux R, Schuller E, Piette JC, Poisson M, Gentilini M, Hauw JJ (1994) AIDS-Related brain lymphomas – clinical study and clinico-pathological correlations. *Revue Neurologique* 2:123–132
2108. Margetts JC, Kalyan-Raman UP (1989) Giant celled glioblastoma of brain: a clinicopathological and radiological study of ten cases (including immunohistochemistry and ultrastructure). *Cancer* 63:524–531
2109. Marguth F, Stammeler A (1963) Diffuse meningeale Karzinomatosen und Sarkomatosen mit der symptomatik intrakranieller Geschwülste. *Zbl Neurochir* 24:59–65
2110. Maria BL, Steek PA, Yung A, Milici A, Bruner JM, Pathaks, Becker FF (1989) The modulation of astrocytic differentiation in cells derived from a medulloblastoma surgical specimen. *J Neurooncol* 7:329–339
2111. Marinesco G, Goldstein M (1933) Sur une forme anatomique, non encore décrite, de médulloblastome: médulloblastome. *Ann Anat Pathol (Paris)* 10:513–525
2112. Mark J, Westermarck B, Pontén J, Hugosson R (1977) Banding patterns in human gliomas cell lines. *Hereditas* 87:243–260
2113. Markesbery WR, Brooks WH, Milsow L, Mortara H (1976) Ultrastructural study of the pineal germinoma in vivo and in vitro. *Cancer* 37:327–337
2114. Markesbery WR, Haug RM, Young AB (1981) Ultrastructure of pineal parenchymal neoplasms. *Acta Neuropathol (Berl)* 55:143–149
2115. Marks JE, Adler SJ (1982) A comparative study of ependymomas by site of origin. *Int J Radiat Oncol Biol Phys* 8:37–43
2116. Marks JE, Baglan RJ, Prasad SC, Blank WF (1981) Cerebral radionecrosis: incidence and risk in relation to dose, time, fractionation and volume. *Int J Radiat Oncol Biol Phys* 7:243–252

2117. Marks JE, Baglan RJ, Wong J (1986) Radiation damage to brain and cranial soft tissues: outcome and incidence before and after reduction in dose. In: Walker MD, Thomas DGT (eds) *Biology of Brain Tumour*. Nijhoff, Boston, pp 325–334
2118. Marks LB, Halperin EC (1995) Radiosurgery is not “standard of care” for solitary brain metastases. *Int J Radiat Oncol Biol Phys* 32:557–558
2119. Markwalder TM, Huber P, Markwalder RV, Seilev RW (1979) Primary intraventricular oligodendrogliomas. *Surg Neurol* 2:25–28
2120. Markwalder TM, Waelti E, König MP (1987) Endocrine manipulation of meningiomas with medroxyprogesterone acetate. Effect of MPA on receptor status of meningioma cytosols. *Surg Neurol* 28:3–9
2121. Markwalder TM, Gerber HA, Waelti E, Schaffner T, Markwalder RV (1988) Hormonotherapy of meningiomas with medroxyprogesterone acetate: immunohistochemical demonstration of the effect of MPA on growth fractions of meningiomas cells using the monoclonal antibody Ki 67. *Surg Neurol* 30:97–101
2122. Márquez-Esteban H, Pérez Villanueva J, Gomez Bueno J, Fernandez Puentes M (1979) Primary intraventricular choriocarcinoma. *Surg Neurol* 11:21–23
2123. Marsa GW, Goffinet DR, Rubinstein LJ, Bagshaw MA (1975) Megavoltage irradiation in the treatment of gliomas of the brain and spinal cord. *Cancer* 36:1681–1689
2124. Marsden HB, Kumar S, Kahn J, Anderton BJ (1983) A study of glial fibrillary brain tumours. *Int J Cancer* 31:439–445
2125. Marsh WL, Stevenson DR, Long HJ (1983) Primary leptomeningeal presentation of T-cell lymphoma. Report of a patient and review of the literature. *Cancer* 51:1125–1131
2126. Marshall AME (1956) An outline of the cytology and pathology of the reticular tissue. Oliver and Boyd, Edinburgh
2127. Marshall CJ (1991) Tumor suppressor genes. *Cell* 64:313–326
2128. Marshall H, Nonchev S, Sham MH, Muchamore I, Lumsden A, Krumlauf R (1992) Retinoic acid alters hindbrain Hox code and induces transformation of rhombomeres 2/3 into a 4/5 identity. *Nature* 360:737–741
2129. Marshall LF, Rorke LB, Schut L (1979) Teratocarcinoma of the brain – a treatable disease? *Childs Brain* 5:96–102
2130. Martin DS, Levy B, Awwad EE, Pittman T (1991) Desmoplastic infantile ganglioglioma: CT and MR features. *AJNR* 12:1195–1197
2131. Martin F, Lemmen LJ (1952) Calcification in intracranial neoplasms. *Am J Pathol* 28:1107–1131
2132. Martin-Achard A, Diserens AC, De Tribolet N, Carrel S (1980) Evaluation of the humoral response of glioma patients to a possible common tumor-associated antigen(s). *Int J Cancer* 25:219–224
2133. Martinez J, Georgoff I, Levine AJ (1991) Cellular localization and cell cycle regulation by a temperature-sensitive p53 protein. *Genes Dev* 5:151–159
2134. Martins AN, Johnson JS, Henry JM, Stoffel TJ, Di Chiro G (1977) Delayed radiation necrosis of the brain. *J Neurosurg* 47:336–345
2135. Martins AN, Severance RE, Henry JM, Doyle TF (1979) Experimental delayed radiation necrosis of the brain. *J Neurosurg* 51:587–596
2136. Martuza RL, Eldridge R (1988) Neurofibromatosis 2 (bilateral acoustic neurofibromatosis). *N Engl J Med* 318:684–688
2137. Martuza RL, Miller DC, MacLaughlin DT (1985) Estrogen and progestin binding by cytosolic and nuclear fractions of human meningiomas. *J Neurosurg* 62:750–756
2138. Martuza RL, Malick A, Markert JM (1991) Experimental therapy of human glioma by means of a genetically engineered virus mutant. *Science* 252:854–855
2139. Marzatico F, Curti D, Dagani F, Silvani V, Gaetani P, Butti G, Knerich R (1986) Enzymes related to energy metabolism in human gliomas. *J Neurosurg Sci* 30:129–132
2140. Mashiyama S, Murakami Y, Yoshimoto T, Sekiya T, Hayashi K (1991) Detection of p53 gene mutation in human brain tumors by single-strand conformation polymorphism analysis of polymerase chain reaction products. *Oncogene* 6:1313–1318
2141. Maspes PE (1934) Emangioblastoma cerebellare. *Riv Pat Nerv Ment* 43:1013
2142. Massagué J (1990) The transforming growth factor- $\beta$  family. *Annu Rev Cell Biol* 6:597–641

2143. Massignan L (1952) Contributo alla conoscenza dei dermoidi ed epidermoidi spinali. *Rass Stud Psich* 41:318–342
2144. Masson P (1956) Les méningiomes In: Masson P (ed) *Les tumeurs humaines*. 2nd edn. Maloine, Paris, pp 977–988
2145. Mastaglia FL, McDonald WI, Watson JV, Jogendran F (1976) Effects of X-radiation on the spinal cord: an experimental study of the morphological changes in central nerve fibres. *Brain* 99:101–122
2146. Mastragostino S (1951) Il carcinoma dei plessi corioidei (osservazioni personali e sintesi bibliografica). *Riv Pat Nerv Ment* 72:465–482
2147. Masuzawa T, Shimabukuro H, Nakahara N, Iwasa H, Sato F (1986) Germ cell tumors (germinoma and yolk sac tumor) in unusual sites in the brain. *Clin Neuropathol* 5:190–202
2148. Mathews T, Moosy J (1972) Mixed glioma, multiple sclerosis and Charcot–Marie–Tooth disease. *Arch Neurol* 27:263–268
2149. Mathewson AJ, Berry M (1985) Observation on the astrocyte response to a cerebral stab wound in adult rats. *Brain Res* 327:61–69
2150. Matrisian LM (1990) Metalloproteinases and their inhibitors in matrix remodelling. *Trends Genet* 6:121–125
2151. Matson DD (1953) Hydrocephalus in a premature infant caused by papilloma of the choroid plexus: with report of surgical treatment. *J Neurosurg* 11:416–420
2152. Matson DD, Crigler JF (1969) Management of craniopharyngioma in childhood. *J Neurosurg* 30:377–390
2153. Matson DD, Crofton FDL (1960) Papilloma of the choroid plexus in childhood. *J Neurosurg* 17:1002–1027
2154. Matsuda M, Hara Y, Watanabe K, Handa J (1989) Huge meningioma in a child. *Surg Neurol* 31:295–299
2155. Matsukada K, Inamura T, Nakano S, Black KL (1995) Enhanced tumor uptake of carboplatin and survival in glioma bearing rats by intracarotid infusion of bradykinin analog, RMP-7. In: *Proc 11th International Conference on Brain Tumor, Research and Therapy*, 31 October–3 November, Silverado, Ca
2156. Matsukado Jm, Curatsu J, Venura S (1987) Immunopathology of leptomeningeal dissemination of brain tumors. *Prog Exp Tumor Res* 30:215–223
2157. Matsukado Y, MacCarty CS, Kernohan JW (1961) The growth of glioblastoma multiforme (astrocytomas grades 3 and 4) in neurosurgical practice. *J Neurosurg* 18:636–644
2158. Matsumoto T, Tani E, Kaba K, Kochi N, Shindo H, Yamamoto Y, Sakamoto H, Furuyama J (1990) Amplification and expression of a multidrug resistance gene in human glioma cell lines. *J Neurosurg* 72:96–101
2159. Matsumoto T, Tani E, Kaba K, Shindo H, Miyaji K (1991) Expression of P-glycoprotein in human glioma cell lines and surgical glioma specimens. *J Neurosurg* 74:460–466
2160. Matsumoto T, Tani E, Yamaura I, Miyaji K, Kaba K (1995) Effects of protein kinase C modulators on multidrug resistance in human glioma cells. *Neurosurgery* 36:565–571
2161. Matsumura A, Ahyai A, Hori A, Schaaake TH (1989) Intracerebral subependymomas. Clinical and neuropathological analyses with special reference to the possible existence of a less benign variant. *Acta Neurochir (Wien)* 96:15–25
2162. Matsumura H, Ross ER (1979) Delayed cerebral radionecrosis following treatment of carcinoma of the scalp: clinicopathologic and ultrastructural study. *Surg Neurol* 12:193–204
2163. Matsuo S (1987) Historadiographic and electron microscopic histochemical studies on acid mucopolysaccharides of experimental gliomas in rats (in Japanese; English abstract)
2164. Matsushima T (1983) Choroid plexus papillomas and human choroid plexus: a light and electron microscopic study. *J Neurosurg* 59:1054–1062
2165. Matsushima T, Fukui M, Egami H (1985) Epithelial cells in a so-called intraspinal neurenteric cyst: a light and electron microscopic study. *Surg Neurol* 24:656–660
2166. Matsushima T, Fukui M, Ohta M, Yamakawa Y, Takaki T, Okano H (1980) Ciliated and goblet cells in craniopharyngiomas. Light and electron microscopic studies at surgery and autopsy. *Acta Neuropathol (Berl)* 50:199–205
2167. Matsutani M, Takakura K, Sano K (1987) Primary intracranial germ cell tumors: pathology and treatment. *Progr Exp Tumor Res* 30:307–312



2168. Mattson RH, Peterson EW (1966) Glioblastoma multiforme of the optic nerve – report of a case. *JAMA* 196:799
2169. Matus A, Mughal S (1975) Immunohistochemical localization of S-100 protein in brain. *Nature* 258:746–748
2170. Maunoury R, Vedrenne C, Constans JP (1975) Infiltrations lymphocytaires dans les gliomes humaines. *Neurochirurgie* (Paris) 21:213–222
2171. Maunoury R, Delpech A, Delpech B, Vidard MN, Védrenne C, Constans JP, Hillerau J (1977) Localisation de la protéine gliofibrillaire (GFAP) par immunocytochimie dans les tumeurs cérébrales humaines. Etude histologique et en culture in vitro. *Neurochirurgie* 23:173–185
2172. Maunoury R, Dumas-Duport C, Fontain C, Vedrenne C (1979) Ultrastructural localization of glial fibrillary acidic protein (GFAP) in human glioma culture by immunoperoxidase method. *Brain Res* 170:392–398
2173. Maurer PK, Ecklund J, Parisi JE, Ondra S (1990) Symptomatic pineal cyst: case report. *Neurosurgery* 27:451–454
2174. Mauro A, Bulfone A (1989) Immunohistochemistry of glial tumors. In: Broggi G, Gerosa MA (eds) *Cerebral gliomas*. Elsevier, Amsterdam pp 133–141
2175. Mauro A, Giordana MT, Migheli A, Schiffer D (1983) Glial fibrillary acidic protein (GFAP) in rat brain tumors transplacentally induced by ethylnitrosourea (ENU). *J Neurol Sci* 61:349–355
2176. Mauro A, Bertolotto A, Giordana MT, Magrassi A, Migheli A, Schiffer D (1983) Biochemical and histochemical evaluation of glycosaminoglycans in brain tumors induced in rats by nitrosourea derivatives. *J Neurooncol* 1:299–306
2177. Mauro A, Sciolla R, Sicuro L, Ponzio R (1983) Solitary neurinoma of the anterior cranial fossa. *J Neurosurg Sci* 27:45–49
2178. Mauro A, Bertolotto A, Germano I, Giaccone G, Giordana MT, Migheli A, Schiffer D (1984) Collagenase in the immunohistochemical demonstration of laminin, fibronectin and Factor VIII/RAG in nervous tissue after fixation. *Histochemistry* 80:157–163
2179. Mauro A, Bulfone A, Turco E, Schiffer D (1991) Coexpression of platelet-derived growth factor (PDGF) B chain and PDGF B-type receptor in human gliomas. *Childs Nerv Syst*, 7:432–436
2180. Mauro A, Di Sapio A, Mocellini C, Schiffer D (1995) Control of meningioma cell growth by platelet-derived growth factor (PDGF). *J Neurol Sci* 131:135–143
2181. Mavroudis C, Townsend JJ, Wilson CB (1977) A metastizing ependymoma of the cauda equina: case report. *J Neurosurg* 47:771–775
2182. Maxwell M, Naber SP, Wolfe HJ, Galanopoulos T, Hedley-Whyte ET, Black P McL, Antoniadis HN (1990) Coexpression of platelet-derived growth factor (PDGF) and PDGF-receptor genes by primary human astrocytomas may contribute to their development and maintenance. *J Clin Invest* 86:131–140
2183. Maxwell M, Galanopoulos T, Hedley-Whyte ET, Black PML, Antoniadis HN (1990) Human meningiomas co-express platelet-derived growth factor (PDGF) and PDGF-receptor genes and their protein products. *Int J Cancer* 46:16–21
2184. Maxwell M, Galanopoulos T, Neville-Golden J, Antoniadis HN (1992) Effect of the expression of transforming growth factor-beta 2 in primary human glioblastomas on immunosuppression and loss of immune surveillance. *J Neurosurg* 76:799–804
2185. May PL, Broome JC, Lawry J, Buxton RA, Battersby RDE (1989) The prediction of recurrence in meningiomas. A flow cytometric study of paraffin-embedded archival material. *J Neurosurg* 71:347–351
2186. Mayo CM, Barron KD (1966) Concurrent glioma and primary intracranial sarcoma. A report of the cases and a review of the literature. *Neurology*, 16:662–672
2187. Mayr E, Diamond LK, Levine RP, Mayr M (1956) Suspected correlation between blood-group frequency and pituitary adenomas. *Science* 124:932–934
2188. Mazza C, Scienza R, Beltramello A, Da Pian R (1991) Cerebral cavernous malformations (cavernomas) in the pediatric age-group. *Childs Nerv Syst* 7:139–146
2189. McCormack BM, Miller DC, Budzilowick G (1992) Treatment and survival of low grade astrocytomas in adults. *Neurosurgery* 31:636–642
2190. McCormick WF (1966) The pathology of vascular (“arteriovenous”) malformations. *J Neurosurg* 24:807–816
2191. McCunniff AJ, Liang MG (1989) Radiation tolerance of the cervical spinal cord. *Int J Radiat Oncol Biol Phys* 16:675–684

2192. McLean CA, Jolley D, Cukier E, Giles G, Gonzales MF (1993) Histopathology 23:249–255
2193. McAllister RM, Isaacs H, Rongey R, Peer M, Au W, Soukup SW, Gardner MB (1977) Establishment of a human medulloblastoma cell line. *Int J Cancer* 20:206–212
2194. McBride OW, Merry D, Givol D (1986) The gene of human p 53 cellular tumor antigen is located on chromosome 17 short arm (17p13). *Proc Natl Acad Sci USA* 83:130–134
2195. McComb JG (1983) Recent research into the nature of cerebrospinal fluid formation and adsorption. *J Neurosurg* 59:369–383
2196. McComb RD, Burger PC (1983) Choroid plexus carcinoma: an ultrastructural and immunohistochemical study. *Cancer* 51:470–475
2197. McComb RD, Bigner DD (1984) The biology of malignant gliomas: A comprehensive survey. *Clin Neuropathol* 3:93–106
2198. McComb RD, Bigner DD (1985) Immunolocalization of laminin in neoplasms of the central and peripheral nervous system. *J Neuropathol Exp Neurol* 44:242–253
2199. McComb RD, Bigner DD (1985) Immunolocalization of monoclonal antibody-defined extracellular matrix antigens in human brain tumors. *J Neurooncol* 3:181–186
2200. McComb JG, Davis RL, Isaacs H Jr (1981) Extraneural metastatic medulloblastoma during childhood. *Neurosurgery* 9:548–551
2201. McComb RD, Jones TR, Pizzo SV, Bigner DD (1982) Specificity and sensitivity of immunohistochemical detection of Factor VIII/von Willebrand factor antigen in formalin-fixed paraffin-embedded tissue. *J Histochem Cytochem* 30:371–377
2202. McComb RD, Jones TR, Pizzo SV, Bigner DD (1982) Immunohistochemical detection of Factor VIII/von Willebrand factor in hyperplastic endothelial cells in glioblastoma multiforme and mixed glioma sarcoma. *J Neuropathol Exp Neurol* 41:479–489
2203. McComb RD, Eastman PJ, Hahn FG, Bennet DR (1987) Cerebellar hemangioblastoma with prominent stromal astrocytosis: diagnosis and histogenetic considerations. *Clin Neuropathol* 6:149–154
2204. McComb RD, Moul JM, Bigner DD (1987) Distribution of type VI collagen in human gliomas: comparison with fibronectin and glioma-mesenchymal matrix glycoprotein. *J Neuropathol Exp Neurol* 46:623–633
2205. McConkey DJ, Fernandez A, Trent II J, Ananthaswamy HN (1995) Oncogene regulation of endonuclease activation in apoptosis. *Cancer Lett* 94:9–16
2206. McCormak BM, Miller DC, Budzilovich G, Voorhees GJ, Ranshoff J (1992) Treatment and survival of low-grade astrocytoma in adults 1977–1988. *Neurosurgery* 31:636–642
2207. McCormick WF, Gerber HW, Mergner WJ (1967) Prolonged survival with extensive astrocytoma. Case report. *J Neurosurg* 27:449–459
2208. McDonald LW, Hayes TL (1967) The role of capillaries in the pathogenesis of delayed radionecrosis of brain. *Am J Pathol* 50:745–758
2209. McFarland DR, Horwitz H, Saenger EL, Behr GK (1969) Medulloblastoma – a review of prognosis and survival. *Br J radiol* 42:198–214
2210. McGinnis W, Krumlauf R (1992) Homeobox genes and axial patterning. *Cell* 68:283–302
2211. McGirr SJ, Ebersold MJ, Scheithauer B, Quast LM, Shaw EG (1988) Choroid plexus papillomas: long term follow-up of a surgically treated series. *J Neurosurg* 69:843–849
2212. McLaughlin JK, Malmer HRS, Blot WJ, Malmer BK, Stone BJ, Weiner JA, Ericsson JLE, Fraumeni JF (1987) Occupational risks for intracranial gliomas in Sweden. *J Natl Cancer Inst* 78:253–257
2213. McLean AJ (1935) Pineal teratomas, with report of a case of operative removal. *Surg* 61:523–527
2214. McLendon RE, Burger PC (1987) The primitive neuroectodermal tumor: a cautionary view. *J Pediatr Neurosci* 3:1–8
2215. McLendon RE, Bigner DD (1994) Immunohistochemistry of the glial acidic protein. Basic and applied consideration. *Brain Pathol* 4:221–228
2216. McLendon RE, Robinson JS, Chambers DB, Grufferman S, Burger PC (1985) The glioblastoma multiforme in Georgia, 1977–1981. *Cancer* 56:894–897
2217. McLone DG, Raimondi AJ, Naidich TP (1982) Craniopharyngiomas. *Childs Brain* 9:188–200
2218. McMahon AP, Joyner AL, Bradley A, McMahon JA (1992) The midbrain-hindbrain phenotype of Wnt-1/Wnt-1 mice results from stepwise deletion of engrailed-expressing cells by 9.5 days postcoitum. *Cell* 69:581–595

2219. McMahon B (1962) Prenatal x-ray exposure and childhood cancer. *J Natl Cancer Inst* 28:1173–1191
2220. McMichael AJ, Andjelkovic DA, Tyroler HA (1976) Cancer mortality among rubber workers: an epidemiologic study. *Ann NY Acad Sci* 271:125–137
2221. McMillan TJ (1993) In vitro radiosensitivity of human medulloblastoma cell lines. *J Neurooncol* 15:91–92
2222. Meadows AT, Massari DJ, Fergusson J, Gordaon J, Littman P, Moss P (1981) Declines in IQ scores and cognitive dysfunctions in children with acute lymphocytic leukaemia treated with cranial irradiation. *Lancet* 2:1015–1018
2223. Mealey J, Chen TT, Shupe R (1974) Response of cultured human glioblastomas to radiation and BCNU chemotherapy. *J Neurosurg* 41:339–349
2224. Mechanick JI, Hochberg FH, LaRocque A (1986) Hypothalamic dysfunction following whole-brain irradiation. *J Neurosurg* 65:745–758
2225. Medema RH, Bos JL (1993) The role of p21ras in receptor tyrosine kinase signalling. *Crit Rev Oncogenesis* 4:615–661
2226. Meeker T, Shiramizu B, Kaplan L, Herndier B, Sanchez H, Grimaldi J, Baumgartner J, Rachlin J, Feigal E, Rosenblum M, McGrath M (1991) Evidence for molecular subtypes of HIV-associated lymphoma: division into peripheral monoclonal, polyclonal and central nervous system lymphoma. *AIDS* 5:669–674
2227. Mehta MP, Masciopinto J, Rozental J, Levin A, Chappell R, Bastin K, Miles J, Turski P, Kubsad S, Mackie T, Kinsella T (1994) Stereotactic radiosurgery for glioblastoma multiforme: report of a prospective study evaluating prognostic factors and analyzing long term survival advantage. *Inter J Radiat Oncol Biol Phys* 30:3 541–549
2228. Meis JM, Ordóñez NG, Runer JM (1986) Meningiomas: an immunohistochemical study of 50 cases. *Arch Pathol Lab Med* 110:934–937
2229. Meis JM, Martz KL, Nelson JS (1991) Mixed glioblastoma multiforme and sarcoma. A clinicopathologic study of 26 radiation therapy oncology group cases. *Cancer* 67:2342–2349
2230. Melamed S, Sahar A, Beller AJ (1979) The recurrence of intracranial meningiomas. *Neurochirurgia* 22:47–51
2231. Mella O (1990) Fractionated hyperthermia in vivo: thermotolerance, sensitivity to BCNU and thermochemosensitivity in the BT<sub>4</sub>A rat glioma. *Int J Hyperth* 6:253–260
2232. Mella O, Dahl O (1985) Timing of combined hyperthermia and 1,3-bis(2-chloroethyl)-1-nitrosourea or cis-diaminedichloroplatinum in BD IX rats with BT<sub>4</sub>A tumors. *Anticancer Res* 5:259–264
2233. Melmon KL, Rosen SW (1964) Lindau's disease. Review of the literature and study of the large kindred. *Am J Med* 36:595–617
2234. Memoli VA, Brown EF, Gould VE (1984) Glial fibrillary acidic protein (GFAP) immunoreactivity in peripheral nerve sheath tumours. *Ultrastruct Pathol* 7:269–275
2235. Mendelsohn MC (1962) Autoradiographic analysis of cell proliferation in spontaneous breast cancer of C3H mouse III. The growth fraction. *J Natl Cancer Inst* 28:1015–1029
2236. Mendenhall NP, Thar TL, Agee OF, Harty-Golder B, Ballinger WE, Millon RR (1983) Primary lymphoma of the central nervous system. Computerized tomography scan characteristics and treatment results for 12 cases. *Cancer* 52:1993–2000
2237. Mendiratta SS, Rosenblum JA, Strobos RJ (1967) Congenital meningiomas. *Neurology* 17:914–918
2238. Meneses AC, Kepes JJ, Sternberger NH (1982) Astrocytic differentiation of neoplastic oligodendrocytes. *J Neuropath Exp Neurol* 41:368
2239. Mennel HD (1972) Gewebekulturuntersuchungen an experimentellerzeugten, transplantierten malignen Neurinomen. *Z Neurol* 201:269–278
2240. Mennel HD, Sato K, Zulch KT (1971) Traumatische Regeneration und Resorptivkarzinogenese am Zentralnervensystem. I. Mitteilung. *Acta Neurochir (Wien)* 25:197–206
2241. Mennel HD, Schairer R, Hayling A (1995) Differential diagnosis of cerebral metastases with a set of cytokeration subtypes. *Clin Neuropathol* 14, 271
2242. Menzies CB, Gunar M, Behan PO (1980) Impaired thymus-derived lymphocyte function in patients with malignant brain tumors. *Clin Neurol Neurosurg* 82:157–168
2243. Mephram BL, Frater W, Mitchell RS (1979) The use of proteolytic enzymes to improve immunoglobulin staining by the PAP technique. *Histochem J* 11:345–357

2244. Mercer WE, Shields MT, Lin D, Appella E, Ullrich SJ (1991) Growth suppression induced by wild type p53 protein is accompanied by selective down-regulation of proliferating-cell nuclear antigen expression. *Proc Natl Acad Sci USA* 88:1958–1962
2245. Merchut PM (1989) Brain metastases from undiagnosed systemic neoplasms. *Arch Intern Med* 149:1076–1080
2246. Merel P, Hoang-Xuan K, Sanson M, Bijlsma E, Rouleau G, Laurent-Puig P, Pulst S, Baser M, Lenoir G, Sterkers JM, Philippon J, Resche F, Mautner VF, Fischer G, Hulsebos T, Aurias A, Delattre O, Thomas G (1995) Screening for germ-line mutations in the NF2 gene. *Genes Chrom Cancer* 12:117–127
2247. Merkel KHH, Hansmann ML (1986) Primary non-Hodgkin's lymphomas of the central nervous system. *Pathol Res Pract* 181:430–433
2248. Merzak A, McCrea S, Koocheckpour S, Pilkington GJ (1994) Control of human glioma cell growth, migration and invasion in vitro by transforming growth factor beta-1. *Br J Cancer* 70:199–203
2249. Merzak A, Parker C, Koocheckpour S, Sherbet GV, Pilkington GJ (1994) Overexpression of the 18A2/mts1 gene and down-regulation of the TIMP-2 gene in invasive human glioma cell lines in vitro. *Neuropathol Appl Neurobiol* 20:614–619
2250. Metheny LJ, Cappione AJ, Skuse GR (1995) Genetic and epigenetic mechanisms in the pathogenesis of neurofibromatosis type I. *J Neuropathol Exp Neurol* 54:753–760
2251. Meyer FB, Sundt TM (1991) Carotid body tumor. In: Wilkins SS, Rengachary SS (eds) *Neurosurgery update II*. McGraw-Hill pp 206–213
2252. Meyer JS, Marchosky JA, Hickey WF (1993) Cell kinetic classification of tumors of the nervous system by DNA precursor labeling in vitro. *Hum Pathol* 24:1357–1364 (7.2.)
2253. Michaud J, Gange F (1983) Microcystic meningioma. Clinico pathologic report of eight cases. *Arch Pathol Lab Med* 107:75–80
2254. Michel MR, Reier PJ (1979) Axonal-ependymal associations during early regeneration of the transected spinal cord in *Xenopus* tadpoles. *J Neurocytol* 8:529–548
2255. Michelsen JJ, New PFJ (1969) Brain tumor and pregnancy. *J Neurol Neurosurg Psychiatry* 32:305–307
2256. Mickle JP (1992) Ganglioglioma in children. A review of 32 cases at the University of Florida. *Pediatr Neurosurg* 18:310–314
2257. Miescher S, Whiteside TL, De Tribolet N, Von Flidner V (1988) In situ characterization, clonogenic potential, and antitumor cytolytic activity of T lymphocytes infiltrating human brain cancers. *J Neurosurg* 68:438–448
2258. Miettinen M, Lehto VP, Dahl D, Virtanen I (1983) Differential diagnosis of chordoma, chondroid and ependymal tumors as aided by antiintermediate filament antibodies. *Am J Pathol* 112:160–169
2259. Miettinen M, Clark R, Virtanen I (1986) Intermediate filament proteins in choroid plexus and ependyma and their tumors. *Am J Pathol* 123:231–240
2260. Migheli A, Mocellini C (1990) Ultrastructural immunocytochemistry in glial tumors. *J Neurosurg Sci* 34:219–222
2261. Migheli A, Attanasio A, Mocellini C, Schiffer D (1991) Ultrastructural localization of Factor VIII-related antigen in endothelial proliferations of malignant gliomas. *Neuropathol Appl Neurobiol* 17:11–16
2262. Migheli A, Cavalla P, Marino S, Schiffer D (1994) A study of apoptosis in normal and pathological nervous tissue after in situ end-labeling of DNA strand breaks. *J Neuropathol Exp Neurol* 53:606–616
2263. Mikhael MA (1980) Dosimetric considerations in the diagnosis of radiation necrosis of the brain. In: Gilbert HA, Kagan AR (eds) *Radiation damage to the nervous system. A delayed therapeutic hazard*. Raven, New York, pp 59–91
2264. Mikhael MA (1980) Radiation necrosis of the brain: correlation between patterns on computed tomography and dose of radiation. *J Comput Assist Tomogr* 3:241–249
2265. Milham S (1985) Mortality in workers exposed to electromagnetic fields. *Environ Health Perspect* 62:297–300
2266. Miller CA, Torack RM (1970) Secretory ependymoma of the filum terminale. *Acta Neuropathol (Berl)* 15:240–250

2267. Miller D, Hochberg F, Harris N, Gruber M, Louis D, Cohen H (1994) Pathology with clinical correlations of primary central nervous system non-Hodgkin's lymphoma. *Cancer* 74:1383-1397
2268. Miller DC, Ojemann RG, Proppe KH, McGinnis BD, Grillo HC (1985) Benign metastasizing meningioma. *J Neurosurg* 62:763-766
2269. Miller DC, Koslow M, Budzilovich GN, Burstein DE (1990) Synaptophysin: a sensitive and specific marker for ganglion cells in central nervous system neoplasms. *Hum Pathol* 21:271-276
2270. Miller RA, Maloney DG, Warnke R, Levi R (1982) Treatment of B-cell lymphoma with monoclonal anti-idiotypic antibody. *N Engl J Med* 306:517-522
2271. Miller RC, McGraig W, Kernohan JW (1952) Supra-tentorial tumors among children. *Arch Neurol Psych* 68:797-814
2272. Miller RH, David S, Patel R, Abney ER, Raff MC (1985) A quantitative immunohistochemical study of macroglial cell development in the rat optic nerve: in vivo evidence of two distinct astrocyte lineages. *Dev Biol* 111:35-41
2273. Miller RM, Raff MC (1984) Fibrous and protoplasmic astrocytes are distinct classes of glial cells. *J Neurosci* 4:585-593
2274. Miller RM, Abuey ER, David S, Constant CF, Lindsay R, Patel R, Stone J, Raff MC (1986) Is reactive gliosis a property of a distinct subpopulation of astrocytes? *J Neurosci* 6:22-29
2275. Millhouse OE (1971) A Golgi study of third ventricle tanocytes in the adult rodent brain. *Z Zellforsch* 127:1-13
2276. Millhouse OE (1972) Light and electron microscopic studies of the ventricular wall. *Z Zellforsch* 127:149-174
2277. Mills PK, Preston-Martin S, Annegers JF, Beeson WL, Phillips RL, Fraser GE (1989) Risk factors for tumors of the brain and cranial meninges in seventh-day adventists. *Neuroepidemiology* 8:266-275
2278. Milstein JM, Geyer JR, Berger MS, Bleyer WA (1989) Favorable prognosis for brainstem gliomas in neurofibromatosis. *J Neurooncol* 7:367-371
2279. Mineta T, Rabkin SD, Yazaki T, Hunter WD, Martuza RL (1995) Attenuated multi-mutated herpes simplex virus-1 for the treatment of malignant gliomas. *Nature Med* 1:938-943
2280. Mirimanoff RO, Dosoretz DE, Linggood RM, Ojemann RG, Martuza RLL (1985) Meningioma: analysis of recurrence and progression following neurosurgical resection. *J Neurosurg* 62:18-24
2281. Mirra SS, Miles ML (1980) Unusual pericytic proliferation in a meningotheliomatous meningioma: An ultrastructural study. *J Neuropathol Exp Neurol* 39:376
2282. Mirra SS, Miles ML (1982) Subplasmalemmal linear density: a mesodermal feature and a diagnostic aid. *Hum Pathol* 13:365-380
2283. Mirra SS, Tindall SC, Check IJ, Brynes RK, Moore WW (1983) Inflammatory meningeal masses of unexplained origin. An ultrastructural and immunological study. *J Neuropathol Exp Neurol* 42:453-468
2284. Mirvish SS (1981) Inhibition of the formation of carcinogenetic N-nitroso compounds by ascorbic acid and other compounds. In: Burchenal JH, Dettgen HF (eds) *Cancer: achievements, challenges and prospects for the 1980's*, vol 1. Grune-Stratton, New York, pp 557-587
2285. Misra BK, Steers AJW, Miller JD, Gordon A (1988) Multicentric glioma presenting with hemorrhage. *Surg Neurol* 29:73-76
2286. Misson JP, Edwards MA, Yamamoto M, Caviness VS jr (1988) Mitotic cycling of radial glial cells of the fetal murine cerebral wall: a combined autoradiographic and immunohistochemical study. *Develop Brain Res* 38:183-190
2287. Misugi K, Liss L (1970) Medulloblastoma with cross-striated muscle. A fine structural study. *Cancer* 25:1279-1285
2288. Mitchell JB, Cook JA, DeGraff W, Glatstein E, Russo A (1989) Keynote address: glutathione modulation in cancer treatment: will it work? *Int J Radiat Oncol Biol Phys* 16:1289-1295
2289. Mittelbach M (1935) Über Gliome mit Metastasen. *Beitr Pathol Anat* 95:538-572
2290. Modan B, Baidatz D, Mart H, Steinitz R, Levin SG (1974) Radiation-induced head and neck tumours. *Lancet* 1:277-279
2291. Modan B, Wagener DK, Feldman JJ (1992) Increased mortality from brain tumors: a combined outcome of diagnostic technology and change of attitude toward the elderly. *Am J Epidemiol* 135:1349-1357

2292. Modis L (1974) Topo-optical investigations of mucopolysaccharides (Acid glycosaminoglycans). In: Graumann W, Neumann K (eds) *Handbuch der Histochemie*, vol. II/4, Fisher, Stuttgart.
2293. Mohan J, Brownell B, Oppenheimer DR (1976) Malignant spread of haemangioblastoma: report of two cases. *J Neurol Neurosurg Psychiatry* 39:515–525
2294. Mohanam S, Sawaja R, McCutcheon I, Ali-Osman F, Boyd D, Rao JS (1993) Modulation of in vitro invasion of human glioblastoma cells by urokinase-type plasminogen activator receptor antibody. *Cancer Res* 53:4143–4147
2295. Molenaar W, Jansson D, Gould VE, Rorke LB, Franke WW, Lee V M-Y, Packer RJ, Trojanowsky JQ (1989) Molecular markers of primitive neuroectodermal tumors and other pediatric central nervous system tumors. Monoclonal antibodies to neuronal and glia antigens distinguish subsets of primitive neuroectodermal tumors. *Lab Invest* 61:635–643
2296. Molnar D, Groothuis D, Blasberg R, Zaharko D, Owens E, Fenstermacher J (1984) Regional thymidine transport and incorporation in experimental brain and subcutaneous tumors. *J Neurochem* 43:421–432
2297. Monacci WT, Merrill MJ, Oldfield EH (1993) Expression of vascular permeability factor/vascular endothelial growth factor in normal rat tissue. *Am J Physiol* 264:C995–1002
2298. Monro P, Mair WGP (1968) Radiation effects on the human central nervous system 14 weeks after X-radiation. *Acta Neuropathol (Berl)* 11:267–274
2299. Monson RR, Fine LJ (1978) Cancer mortality and morbidity among rubber workers. *J Natl Cancer Inst* 61:1047–1053
2300. Monticone GF, Fabiani A, Schiffer D (1966) Aspetti istochimici delle strutture lisosomiche nelle cellule gliali. *Boll Soc Ital Biol Sper* 42:1207–1208
2301. Moody SA, Quigg MS, Frankfurter A (1989) The development of the peripheral trigeminal system in the chick embryo revealed by an isotype specific anti-b-tubulin monoclonal antibody. *J Comp Neurol* 279:567–580
2302. Moore RY, Klein DC (1974) Visual pathways and the central neural control of a circadian rhythm in pineal serotonin N-acetyltransferase activity. *Brain Res* 71:17–33
2303. Moraci A, Cioffi F (1976) Le méningiome kystique: aboutissement de la “forme humide” de Masson. *Neurochirurgie* 22:701–710
2304. Morantz RA (1987) Radiation therapy in the treatment of cerebral astrocytoma. *Neurosurgery* 20:975–982
2305. Morantz RA (1991) Trauma and demyelination as etiologic factors in the development of brain tumor. In: Salzman M (ed) *Neurobiology of brain tumors*. Williams and Wilkins, Baltimore, pp 73–84
2306. Morantz RA, Shain W (1978) Trauma and brain tumors: an experimental study. *Neurosurgery* 3:181–186
2307. Morantz RA, Feigin I, Ransohoff J (1976) Clinical and pathological study of 24 cases of gliosarcoma. *J Neurosurg* 45:398–408
2308. Morantz RA, Wood GW, Foster M, Clark M, Gollahonxk (1979) Macrophages in experimental and human brain tumors. Part 2: Studies of the macrophage content of human brain tumors. *J Neurosurg* 50:305–311
2309. Morantz RA, Kepes JJ, Batnitzky S, Masterson BJ (1979) Extrapapillary ependymomas. Report of three cases. *J Neurosurg* 51:383–391
2310. Morelli RJ (1966) Intracranial neurilemmoma of the hypoglossal nerve. *Neurology* 16:709–713
2311. Morello G, Lombardi G (1964) Choroido-ependymal cyst of the spinal root: case report. *J Neurosurg* 21:1103–1107
2312. Morello G, Migliaavacca F (1964) Primary choroid papillomas in the cerebello-pontine angle. *J Neurol Neurosurg Psychiatry* 27:445–450
2313. Morgan KT, Johnson BP, Frith CH, Townsend J (1982) An ultrastructural study of spontaneous mineralization in the brains of aging mice. *Acta Neuropathol (Berl)* 58:120–124
2314. Morgello S (1995) Pathogenesis and classification of primary central nervous system lymphoma: an update. *Brain Pathol* 5:383–393
2315. Morgello S, Maiese K, Petito CK (1989) T-cell lymphoma in CNS: chemical and pathologic features. *Neurology* 39:1190–1196

2316. Mori K, Handa H, Murata T, Johikawa M, Takeudi T (1980) Craniopharyngiomas with unusual topography and associated with vascular pathology. *Acta Neuropathol (Berl)* 53:53–68
2317. Mori K, Handa H, Murata T, Takeudi J, Miwa S, Osake K (1980) Results of treatment for craniopharyngioma. *Childs Brain* 6:303–312
2318. Mori O, Maschisuka M, Sakamoto F, Nomura H, Sasai Y (1988) Immunohistochemical observation of S100 protein and neuron specific enolase in cells of granular cell tumor. *Acta Histochem* 83:33–38
2319. Mori S, Leblond CP (1970) Electron microscope identification of three classes of oligodendrocytes and a preliminary study of their proliferative activity in the corpus callosum of young rats. *J Comp Neurol* 139:1–30
2320. Mori T, Nagase H, Horii A, Miyoshi Y, Shimano T, Nakatsuru S, Aoki T, Arakawa H, Yanagisawa A, Ushio Y, Takano S, Ogawa M, Nakamura M, Schibuya M, Mishikawa R, Matsutani M, Hayaschi Y, Takahashi H, Ikuta F, Nishihira T, Mori S, Nakamura Y (1994) Germ-line and somatic mutations of the APC gene in patients with Turcot syndrome and analysis of APC mutations in brain tumors. *Genes Chrom Cancer* 9:168–172
2321. Morild I, Mork S, Nyland H (1982) Metastasizing neuroectodermal tumour. *J Neurol* 227:151–155
2322. Morimura T, Kitz K, Budka H (1989) In situ analysis of cell kinetics in human brain tumors. A comparative immunocytochemical study of S-phase cells by a new in vitro bromodeoxyuridine-labeling technique, and of proliferating pool cells by monoclonal antibody Ki-67. *Acta Neuropathol (Berl)* 77:276–282
2323. Mörk SJ, Laerum OD (1980) Modal DNA content of human intracranial neoplasms studied by flow cytometry. *J Neurosurg* 53:198–204
2324. Mörk SJ, Loken AC (1977) Ependymoma: a follow-up study of 101 cases. *Cancer* 40:907–915
2325. Mörk SJ, Rubinstein LJ (1985) Ependymblastoma: a reappraisal of a rare embryonal tumor. *Cancer* 55:1536–1542
2326. Mörk SJ, Rubinstein LJ (1988) Metastatic carcinoma to glioma. A report of three cases with a critical review of the literature. *J Neurol Neurosurg Psychiatry* 51:256–261
2327. Mörk SJ, Nyland H, Matre R, Ganz J (1985) Characterization of host mononuclear cells in gliomas. *J Neuropathol Exp Neurol* 44:317
2328. Mörk SJ, Lindegaard K-F, Halvorsen TB, Lehmann EH, Solgaard T, Hatlevoli R, Harvel S, Ganz J (1985) Oligodendroglioma: incidence and biological behavior in a defined population. *J Neurosurg* 63:881–889
2329. Mörk SJ, Halvorsen TB, Lindegaard KF, Eide GE (1986) Oligodendroglioma. Histologic evaluation and prognosis. *J Neuropathol Exp Neurol* 45:65–78
2330. Mörk SJ, Rubinstein LJ, Kepes JJ (1988) Patterns of epithelial metaplasia in malignant gliomas. I Papillary formations mimicking medulloepithelioma. *J Neuropathol Exp Neurol* 47:93–100
2331. Mörk SJ, Rubinstein LJ, Kepes JJ, Perentes E, Uphoff DF (1988) Patterns of epithelial metaplasia in malignant gliomas. II Squamous differentiation of epithelial-like formation in gliosarcomas and glioblastomas. *J Neuropathol Exp Neurol* 47:101–118
2332. Morley TP (1958) The morphology of meningiomas grown in culture. *J Neuropathol Exp Neurol* 17:635–643
2333. Morley TP (1959) The recovery of tumor cells from venous blood draining cerebral gliomas: a preliminary report. *Can J Surg* 2:363–365
2334. Morrison RS, Yamaguchi F, Saya H, Bruner JM, Yahanda AM, Donehower LA, Berger M (1994) Basic fibroblast growth factor and fibroblast growth factor receptor I are implicated in the growth of human astrocytomas. *J Neurooncol* 18:207–216
2335. Mosberg WH, Blackwood W (1954) Mucus-secreting cells in colloid cysts of the third ventricle. *J Neuropathol Exp Neurol* 13:417–426
2336. Moss SD, Rockswold GL, Chou SN, Yock D, Berger MS (1988) Radiation-induced meningiomas in pediatric patients. *Neurosurgery* 22:758–761
2337. Moss TH (1984) Observations on the nature of subependymoma: an electron microscopic study. *Neuropathol Appl Neurobiol* 10:63–75
2338. Motoi M, Yoshino T, Hayashi K, Nose S, Harie Y, Ogawa K (1985) Immunohistochemical studies on human brain tumors using anti-Leu7 monoclonal antibody in paraffin-embedded specimens. *Acta Neuropathol (Berl)* 66:75–77

2339. Motomochi M, Makita Y, Nabeshima S, Aoyama I (1980) Spinal epidural meningioma in childhood. *Surg Neurol* 13:5–7
2340. Mufson JA, Davidoff LM (1944) Multiple meningiomas. Report of two cases. *J Neurosurg* 1:45–57
2341. Mukai K, Rosai J (1984) Factor VIII-related antigen: an endothelial marker. In: De Lellis RA (ed) *Advances in immunohistochemistry*. Masson, New York, pp 253–261
2342. Mukai M (1983) Immunohistochemical localization of S100 protein and peripheral nerve myelin (P2 protein; P0 protein) in granular cell tumors. *Am J Pathol* 112:139–146
2343. Mukai M, Torikata C, Iri H, Morikawa Y, Shimizu K, Shimoda T, Nukina N, Ihara Y, Kapeyama K (1985) Expression of neurofilament triplet proteins in human neural tumors. *Am J Pathol* 122:28–35
2344. Mukai N, Murao T (1975) Retinal tumor induction by ocular inoculation of human adenovirus in 3-day-old rats. *J Neuropathol Exp Neurol* 34:28–35
2345. Mukai N, Nakajima T, Fredro T, Jacobson M, Dunn M (1977) Retinoblastoma-like neoplasms induced in C3H/BifB/Ki strain mice by human adenovirus serotype 12. *Acta Neuropathol (Berl)* 39:147
2346. Müller H (1858) Über das Vorkommen von Resten der Chorda dorsalis bei Menschen nach der Geburt und über ihr Verhältnis zu den Gallertgeschwülsten am Clivus. *Z Rat Med* 2:202–229
2347. Müller J, Mealey J (1971) The use of tissue culture in differentiation between angioblastic meningioma and hemangiopericytoma. *J Neurosurg* 34:341–348
2348. Müller W (1962) Über das Pigment im Neurinom. *Dtsch Zbl Nervenheilk* 183:331–339
2349. Müller W (1965) Untersuchung über die Lipotide im Neurinom. *Verh Dtsch Ges Path* 49:338–341
2350. Müller W (1976) Beitrag zur topistischen Einteilung der Kraniopharyngiome. *Acta Neurochir (Wien)* 33:83–91
2351. Müller W, Dahmen HG (1978) Granular cell tumor of the optic nerve. *Graefes Arch Clin Exp Ophthalmol* 207:181–187
2352. Müller W, Schaefer HE (1974) Beitrag zur morphologischen Onkotypie des Medulloblastoms. *Acta Neuropathol (Berl)* 30:51–61
2353. Müller W, Afra D, Schröder R (1977) Supratentorial recurrences of gliomas: morphological studies in relation to time intervals with oligodendrogliomas. *Acta Neurochir (Wien)* 39:15–25
2354. Müller W, Bramisch R, Afra D, Schwenzfeger A (1977) Cytophotometrische Messungen des DNS-Gehaltes in Ependymomen und Plexuspapillomen. *Acta Neuropathol (Berl)* 39:255–259
2355. Mulligan RC (1993) The basic science of gene therapy. *Science* 260:926–931
2356. Mulligan RM (1950) Chemodectoma in the dog. *Am J Path* 26:680–681
2357. Munch-Petersen CJ (1949) A case of disseminated sclerosis and glioma of the brain in the same patient. *Acta Psychiat Neurol* 24:599–605
2358. Mundinger F (1986) Stereotactic biopsy and technique of implantation (instillation) of radionuclids. In: Jellinger K (ed) *Therapy of malignant brain tumors*. Springer, Vienna New York
2359. Murovic J, Turowski K, Wilson CB, Hoshino T, Levin VA (1986) Computerized tomography in the prognosis of malignant cerebral gliomas. *J Neurosurg* 65:799–806
2360. Murphy MD, Dhalla SS, Diocee M, Halliday W, Wiserman NE, Desa DJ (1987) Congenital ependymoblastoma presenting as a sacrococcygeal mass in a newborn: an immunohistochemical, light and electron microscopic study. *Clin Neuropathol* 6:162–173
2361. Murray KJ, White JG, Douglas SD (1980) Comparative biochemical and ultrastructural studies of capillaries from normal humans, normal mice, and human cerebral astrocytomas. *Surg Neurol* 14:53–58
2362. Murray KJ, Kun LM, Cox J (1986) Primary malignant lymphoma of the central nervous system. Results of treatment of 11 cases and review of the literature. *J Neurosurg* 65:600–607
2363. Murray MR (1942) Comparative data on tissue cultures of acoustic neurilemmomas and meningiomas. *J Neuropathol Exp Neurol* 1:123–124
2364. Murray MR, Stout AP (1940) Schwann cells versus fibroblasts as the origin of the specific nerve sheaths tumors. Observations upon normal nerve sheaths and neurilemmoma in vitro. *Am J Pathol* 16:41–60



2365. Musicco M, Filippini G, Bordo BM, Melotto A, Morello G, Berrino F (1982) Gliomas and occupational exposure to carcinogens: case-control study. *Am J Epidemiol* 116:782-790
2366. Musicco M, Sant M, Molinari S, Filippini G, Gatta G, Berrino F (1988) A case-control study of brain gliomas and occupational exposure to chemical carcinogens: the risk to farmers. *Am J Epidemiol* 128:778-785
2367. Musolino A, Munari C, Blond S, Betti O, Lajat Y, Schaub C, Askienezy S, Chodkiewicz JP (1985) Traitement stéréotaxique des kystes expansifs de craniopharyngiomes par irradiation endocavitaire beta (Re 186; Au 198, Y 90). *Neurochirurgie* 31:169-178
2368. Mussini JM, Friol M, De Kersaint-Gilly A, Nomballais MF, Mathi JF, Mayne C, Feve JR (1980) Radionécrose cérébrale découverte 32 ans après irradiation conventionnelle pour adénome hypophysaire. *Rev Neurol (Paris)* 1:43-58
2369. Nabi IV, Watanabe H, Silletti S, Raz A (1991) Tumor cell autocrine motility factor receptor. In: Goldberg ID (ed) *Cell motility factors*. Berkhauser, Basel, pp 163-177
2370. Nabors MW, Griffin CA, Zehnbauser BA, Hruban RH, Philips PC, Grossman SA, Brem H, Colvin OM (1991) Multidrug resistance gene (MDR1) expression in human brain tumors. *J Neurosurg* 75:941-946
2371. Naganuma H, Inoue H, Misumi S, Nakamura M, Tamura M (1984) Intracranial germ-cell tumors. Immunohistochemical study of three autopsy cases. *J Neurosurg* 61:931-937
2372. Naganuma H, Onoue HK, Nakamura M, Koizumi H (1985) Localization of carcinoembryonic antigen in mature intracranial teratomas. *J Neurosurg* 62:870-873
2373. Naganuma H, Sasaki A, Satoh E, Sakihama T, Tasaka K, Nukui H (1994) Improved bioassay for the detection of transforming growth factor-beta1 and beta2 in malignant gliomas. *Neurol Med Chir* 34:143-149
2374. Nagasaka S, Kuromatsu C, Wakisaka S, Kitamura K, Matsushima T (1981) Rathke's cleft cyst. *Surg Neurol* 15:402-405
2375. Nagasaka S, Tanabe KK, Bruner JM, Saya H, Sawaya RE, Morrison RS (1995) Alternative RNA splicing of the hyaluronic acid receptor. CD44 in the normal human brain and in brain tumors. *J Neurosurg* 82:858-863
2376. Nagasawa S, Handa H, Yamashita J, Kinuta Y (1983) Dense cystic craniopharyngioma with unusual extensions. *Surg Neurol* 19:299-301
2377. Nagashima C, Nakashio K, Fujino T (1963) Meningioma and astrocytoma adjacent in the brain. *J Neurosurg* 20:995-999
2378. Nagashima K, Shinohara T, Tokuchi F, Tanaka S, Matsuda M, Yasui K (1990) Viral neurooncogenesis in JC virus-medulloblastoma study. *Proc XI Intern Congr Neuropathol*, 2-8 September, Kyoto, Japan, pp 28
2379. Nagashima N, Goto K, Tsukidate K, Sobue M, Toida M, Takeuchi J (1983) Choroid plexus papilloma. Light and electron microscopic study. *Virchows Arch [A]* 400:201-211
2380. Nagashima T, Hoshino T (1985) Rapid detection of S-phase cells by anti-bromodeoxyuridine monoclonal antibody in 9L brain tumor cells in vitro and in situ. *Acta Neuropathol (Berl)* 66:12-17
2381. Nagashima T, Hoshino T, Cho KG, Senegor M, Waldman F, Nomura K (1988) Comparison of bromodeoxyuridine labeling indices obtained from tissue sections and flow cytometry of brain tumors. *J Neurosurg* 68:388-392
2382. Nagashima T, Hoshino T, Cho KG, Edwards MSB, Hudgins RJ, Davis RL (1988) The proliferative potential of human ependymomas measured by in situ bromodeoxyuridine labeling. *Cancer* 61:2433-2438
2383. Nahser HC, Grote W, Löhr E, Gerhard L (1981) Multiple meningiomas. Clinical and computed tomographic observations. *Neuroradiology* 21:259-263
2384. Naito M, Naito T, Ito A (1984) Spinal cord tumors induced by N-ethyl-N-nitrosourea in rats: presence of spinal subpial cells. *J Natl Cancer Inst* 72:715-724
2385. Nakagawa Y, Perentes E, Rubinstein LJ (1986) Immunohistochemical characterization of oligodendrogliomas: an analysis of multiple markers. *Acta Neuropathol (Berl)* 72:15-22
2386. Nakagawa Y, Perentes E, Ross GW, Ross AN, Rubinstein LJ (1988) Immunohistochemical differences between intracranial germinoma and their gonadal equivalents. An immunoperoxidase study of germ cell tumours with epithelial membrane antigen, cytokeratin and vimentin. *J Pathol* 156:67-72

2387. Nakajima T, Watabane S, Sato Y, Kaneya T, Hirota T, Shimosato Y (1982) An immunoperoxidase study of S-100 protein distribution in normal and neoplastic tissues. *Am J Surg Pathol* 6:715-727
2388. Nakajima T, Kameya T, Watabane S, Hirota T, Shimosato Y, Isobe T (1984) S-100 protein distribution in normal and neoplastic tissues. In: De Lellis RA (ed) *Advances in immunohistochemistry*. Masson, New York, pp 141-158
2389. Nakamura T, Hara M, Kasuga T (1989) Transplacental induction of peripheral nervous tumor in the Syrian golden hamster by N-nitroso-N-ethylurea. *Am J Pathol* 135:251-259
2390. Nakamura Y, Becker LE (1983) Subependymal giant-cell tumor: astrocytic or neuronal? *Acta Neuropathol (Berl)* 60:271-277
2391. Nakamura Y, Becker LE, Marks A (1983) Distribution of immunoreactive S-100 protein in pediatric brain tumors. *J Neuropathol Exp Neurol* 43:136-145
2392. Nakamura Y, Nakashima T, Komatsu Y, Hashimoto T, Hachisuka H (1984) Striated muscle cells in the leptomeninges: an immunohistochemical study. *Arch Pathol Lab Med* 108:561-563
2393. Nakano T, Iwabuchi K, Yagishita S, Itoh Y (1984) An autopsy case of cerebral calcification, with special reference to the morphogenesis of the calcified deposits. *Brain Nerve* 36:151-158
2394. Nakasu S, Hirano A, Llena J, Shimura T, Handa J (1989) Interface between the meningioma and the brain. *Surg Neurol* 32:206-212
2395. Nakasu S, Nakasu Y, Nioka H, Nakajima M, Hamda J (1994) Bcl.2 protein expression in tumors of the central nervous system. *Acta Neuropathol* 88:520-526
2396. Napolitano L, Kyle R, Fischer ER (1963) Ultrastructure of meningiomas and the derivation and nature of their cellular components. *Cancer* 17:233-241
2397. Nasca PC, Baptiste MS, McCubbin PA, Metzger BB, Carlton K, Greenwald P, Armbrustmacher VW, Earle KM, Waldman J (1988) An epidemiologic case-control study of central nervous system tumors in children and parental occupational exposures. *Am J Epidemiol* 128:1256-1265
2398. Nasu H, Müller W (1964) Enzymhistochemische Untersuchungen an Gliomen. *Dtsch Ztsch Nervenheilk* 186:67-86
2399. Nathaniel EJH, Nathaniel DR (1981) The reactive astrocytes. In: Fedoroff S, Hertz L (eds) *Advances in cellular neurobiology*. Academic, New York, vol 2, pp 249-301
2400. Neglia JP, Meadows AT, Robison LL, Kim TH, Newton WA, Ruymann FB, Sather HN, Hammond GD (1991) Second neoplasms after acute lymphoblastic leukemia in childhood. *N Engl J Med* 325:1330-1336
2401. Nelson DF, Nelson JS, Davis DR, Huai Chang C, Griffin TW, Pajak TF (1985) Survival and prognosis of patients with astrocytoma with atypical or anaplastic features. *J Neurooncol* 3:99-103
2402. Nelson JS, Zukada Y, Schoenfeld D, Fulling K, Lamarche J, Peress N (1983) Necrosis as a prognostic criterion in malignant supratentorial astrocytic gliomas. *Cancer* 52:550-554
2403. Netsky MG (1964) Experimental induction and transplantation of brain tumours in animals. In: Zülck KJ, Woolf AI (eds) *Classification of brain tumours*. Springer, Vienna, p 46
2404. Neufeld G, Gospodarowicz D (1988) Identification of the fibroblast growth factor receptor in human vascular endothelial cells. *J Cell Physiol* 136:537-542
2405. Neumann HPH (1987) Basic criteria for clinical diagnosis and genetic counselling in von Hippel-Lindau syndrome. *J Vasc Dis* 16:220-226
2406. Neumann HPH, Eggert HR, Weigel K, Friedburg H, Wiestler O, Schollmeyer P (1989) Hemangioblastomas of the central nervous system. A 10-year study with special reference to von Hippel-Lindau syndrome. *J Neurosurg* 70:24-30
2407. Neumann HPH, Eggert HR, Scheremet R, Schumacher M, Mohadjer M, Walkhloo AK, Volk B, Hettmannsperger U, Riegler P, Schollmeyer P, Wiestler O (1992) Central nervous system lesions in von Hippel-Lindau syndrome. *J Neurol Neurosurg Psychiatr* 55:898-901
2408. Neumann HPH, Lips CJM, Hsia YE, Zbar B (1995) Von Hippel-Lindau syndrome. *Brain Pathol* 5:181-193
2409. Neuwelt EA (1984) Therapeutic potential for blood brain barrier modification in malignant brain tumors. *Prog Exp Tumor Res* 28:51-66

2410. Neuwelt EA (1986) The blood-brain barrier: does its disruption have a role in the treatment of central nervous system neoplasm? In: Neuwelt E (ed) The clinical impact of the blood-brain barrier and its manipulation. Plenum, New York, pp 115–170
2411. Neuwelt EA, Glasberg M, Frenkel E (1983) Neurotoxicity of chemotherapeutic agents after blood-brain barrier modification: neuropathological studies. *Ann Neurol* 14:316–324
2412. Neuwelt EA, Nazzaro JM (1990) The role of surgery in the management of supratentorial intermediate and high-grade astrocytomas in adults. *J Neurosurg* 73:331–344
2413. Neuwelt EA, Smith RG (1979) Presence of lymphocyte membrane surface markers on “small cells” in a pineal germinoma. *Ann Neurol* 6:133–139
2414. Neuwelt EA, Baleban E, Diehl J, Hill S, Frenkel E (1983) Successful treatment of primary central nervous system lymphomas with chemotherapy after osmotic blood-brain barrier opening. *Neurosurgery* 12:662–671
2415. Neuwelt EA, Buchan C, Blank NK, Lewy AJ (1985) Surgical resection of pineal tumor containing elements of germinoma and astrocytoma. *Neurosurgery* 16:373–378
2416. Neuwelt EA, Frenkel EP, Gumerlock MK, Brazier R, Dana B, Hill SA (1986) Development in the diagnosis and treatment of primary CNS lymphoma. A prospective series. *Cancer* 58:1609–1620
2417. Neuwelt EA, Goldman DL, Dahlborg SA, Crossen J, Ramsey F, Roman-Goldstein S, Brazier R, Dana B (1991) Primary CNS lymphoma treated with osmotic blood-brain barrier disruption: prolonged survival and preservation of cognitive function. *J Clin Oncol* 9:1580–1590
2418. Nevin S (1938) Gliomatosis cerebri. *Brain* 61:170–191
2419. New PFJ, Hesselink JR, O’Carroll CP, Kleinman GM (1982) Malignant meningiomas: CT and histologic criteria, including a new CT sign. *AJNR* 3:267–276
2420. Newcomb EW, Madonia WJ, Pisharody S, Lang FE, Koslow M, Miller DC (1993) A correlative study of p53 protein alteration and p53 gene mutation in glioblastoma multiforme. *Brain Pathol* 3:229–235
2421. Newman HFV, Bleeher NM, Ward R, Workman P (1988) Hypoxic cell radiosensitizers in the treatment of high grade gliomas: a new direction using combined R<sub>0</sub>-8799 (pimonidazole) and SR 2508 (etanidazole). *Int J Radiat Oncol Biol Phys* 15:677–684
2422. Ng H-K (1988) Diffuse gliomatosis of the central nervous system with histological features of microgliomatosis. *Clin Neuropathol* 7:266–270
2423. Ng THK, Fung CF, Ma LT (1990) The pathological spectrum of desmoplastic infantile ganglioglioma. *Histopathology* 16:235–241
2424. Nicholson GL, Brunson KW, Fidler IJ (1978) Specificity of arrest, survival and growth of selected metastatic variant cell lines. *Cancer Res* 38:4105–4111
2425. Nicholson WJ, Seidman H, Selikoff IJ (1982) Brain tumors among operating engineers in the chemical and petrochemical industry in Texas and Louisiana. *Ann NY Acad Sci USA* 381:172–180
2426. Nicola N, Thal HO (1983) Multiple Meningeome in verschiedenen Etagen der zerebro-medullären Achse. *Neurochirurgia* 26:120–123
2427. Nielsen SL, Wilson CB (1975) Ultrastructure of a “pineocytoma”. *J Neuropathol Exp Neurol* 34:148–158
2428. Nigro JM, Baker SJ, Preisinger AC, Jessup JM, Hostetter R, Cleary K, Bigner SH, Davidson N, Baylin S, Devilee P, Glover T, Collins FS, Weston A, Modali R, Harris CC, Vogelstein B (1989) Mutations in the p53 gene occur in diverse human tumor types. *Nature* 342:705–708.
2429. NIH Consensus Development Conference Statement (1988) Neurofibromatosis. *Arch Neurol* 45:575–578
2430. Nikitin AY, Ballering LAP, Lyons J, Rajewsky MF (1991) Early mutation of the neu (erb B-2) gene during ethylnitrosurea-induced oncogenesis in the rat Schwann cell lineage. *Proc Natl Acad Sci USA* 88:9939–9943.
2431. Nilsson S, Carlsson J, Larson B, Ponten J (1980) Survival of irradiated glia and glioma cells studied with a new cloning technique. *Int J Radiat Biol* 37:267–279
2432. Nirankari MS, Gleer CH, Chaddah MR (1963) Malignant non-chromaffin paraganglioma in the orbit. *Br J Ophthalmol* 47:357–363
2433. Nisen PD, Zimmerman KA, Cotter SV, Gilbert F, Alt FW (1986) Enhanced expression of the N-myc gene in Wilms’ tumors. *Cancer Res* 46:6217–6222

2434. Nishi T, Lee PS, Oka K, Levin VA, Tanase S, Morino Y, Saya H (1991) Differential expression of two types of the neurofibromatosis type 1 (NF-1) gene transcripts related to neuronal differentiation. *Oncogene* 6:1555–1559
2435. Nishio S, Korosue K, Tateishi J, Fukui M, Kitamura K (1982) Ventricular and subarachnoid seeding of intracranial tumors of neuroectodermal origin. A study of 26 consecutive autopsy cases with reference to focal ependymal defect. *Clin Neuropathol* 1:83–91
2436. Nishio S, Otha M, Abe M, Kitamura K (1983) Microvascular abnormalities in ethylnitrosourea (ENU)-induced rat brain tumors: structural basis for altered blood-brain barrier function. *Acta Neuropathol (Berl)* 59:1–10
2437. Nishio S, Takeshita I, Fukui M, Yamashita M, Tateishi J (1988) Anaplastic evolution of childhood optic-hypothalamic pilocytic astrocytoma: report of an autopsy case. *Clin Neuropathol* 7:254–258
2438. Nishio S, Tashima T, Takeshita I, Fukui M (1988) Intraventricular neurocytoma: clinicopathological features of six cases. *J Neurosurg* 68:665–670
2439. Nishio S, Fujiwara S, Aiko Y, Takeshita I, Fukui M (1989) Hypothalamic hamartoma. Report of two cases. *J Neurosurg* 70:640–645
2440. Nistér M, Libermann TA, Betsholtz C, Pettersson M, Claesson-Welsh L, Heldin C-H, Schlessinger J, Westermark B (1988) Expression of messenger RNAs for platelet-derived growth factor and transforming growth factor- $\alpha$  and their receptors in human malignant glioma cell lines. *Cancer Res* 48:3910–3918
2441. Nitta T, Sato K, Okumura K (1991) Transforming growth factor (TGF)- $\beta$ -like activity of intracranial meningioma and its effect on cell growth. *J Neurol Sci* 101:19–23
2442. Nixon JR, Houser OW, Gomez MR, Okazaki H (1989) Cerebral tuberous sclerosis: MR imaging. *Radiology* 170:869–873
2443. Nixon JR, Miller GM, Okazaki H, Gomez MR (1989) Cerebral tuberous sclerosis. Postmortem magnetic resonance imaging and pathologic anatomy. *Mayo Clin Proc* 64:305–311
2444. Nobile-Orazio E, Hays AP, Latov N, Perman G, Golier S, Shy ME, Fredo L (1984) Specificity of mouse and human monoclonal antibodies to myelin-associated glycoprotein. *Neurology* 34:1336–1342
2445. Noble M, Murray K, Stroobant P, Waterfield MD, Riddle P (1988) Platelet-derived growth factor promotes division and motility and inhibits premature differentiation of the oligodendrocyte/type 2 astrocyte progenitor cell. *Nature* 333:560–562
2446. Nobori T, Miura K, Wu DJ, Lois A, Takabayashi K, Carson DA (1994) Deletions of the cyclin-dependent kinase-4 inhibitor gene in multiple cancers. *Nature* 368:753–756
2447. Noetzel H, Rox J (1964) Autoradiographische Untersuchungen über Zellteilung und Zellentwicklung im Gehirn der erwachsenen Maus und des erwachsenen Rhesus-Affen nach Injektion von Radioaktiven Thymidin. *Acta Neuropathol (Berl)* 3:326–342
2448. Noetzel M, Malamud N (1962) Post-irradiation gliosarcoma of the brain. *Cancer* 15:617–622
2449. Noltenius C, Noltenius H (1985) Dormant tumor cells in liver and brain. An autopsy study on metastasizing tumors. *Pathol Res Pract* 179:504–510
2450. Nomura K (1990) Statistical analysis of malignant glioma in Japan. Symposium on Brain Tumor Pathology, 9–10 September, Biwako, Japan, p 83
2451. Nordlund ML, Rizvi TA, Brannan CI, Ratner N (1995) Neurofibromin expression and astrogliosis in neurofibromatosis (Type 1) brains. *J Neuropath Exp Neurol* 54:588–600
2452. Norenberg MD (1979) The distribution of glutamine synthetase in the rat central nervous system. *J Histochem Cytochem* 27:756–762
2453. Norenberg MD (1994) Astrocyte responses to CNS injury. *J Neuropathol Exp Neurol* 53:213–220
2454. Norenberg MD, Martinez-Hernandez A (1979) Fine structural localization of glutamine synthetase in astrocytes of rat brain. *Brain Res* 161:303–310
2455. Norgaard-Pedersen LJ, Albrechtsen R, Teilum G (1978) Alpha-fetoprotein and human chorionic gonadotropin in a patient with a primary intracranial germ cell tumor. *Cancer* 41:2315–2320
2456. Norman P, Diamond C, Boyd D (1978) Relative detectability of intracranial calcifications on computed tomography and skull radiography. *J Comput assist Tomogr* 2:61–63
2457. North CA, North RB, Epstein JA (1990) Low grade cerebral astrocytomas. Survival and quality of life after radiation therapy. *Cancer* 66:6–14

2458. Northfield DWC, Russell DS (1967) Pubertas praecox due to hypothalamic hamartoma: report of two cases surviving removal of tumour. *J Neurol Neurosurg Psychiatry* 30:160–173
2459. Noske W, Leutzen H, Lange K (1982) Phagocytotic activity of glial cells in culture. *Exp Cell Res* 142:437–445
2460. Notohara K, Hauch CL, Awai M (1990) Glial fibrillary acidic protein immunoreactivity of chondrocytes in immature and mature teratomas. *Acta Pathol Jpn* 40:335–342
2461. Nugent JL, Bunn PA, Rattherwes MJ et al (1979) CNS metastases in small cell bronchogenic carcinoma. Increasing frequency and changing pattern with lengthening survival. *Cancer* 44:1885–1893
2462. Numaguchi Y, Hoffman JC, O' Brien MS, Fukui M, Matsuura K, Kitamura K (1978) Meningiomas in childhood and adolescence. *Neurol Med Chir* 18:119–127
2463. Nusse R, Varmus HE (1992) Wnt genes. *Cell* 69:1073–1087
2464. Nutt CL, Costello JF, Banbrink LL, Yarosh DB, Swinnen LJ, Chambers AF, Cairncross JG (1995) O-6-methylguanine-DNA methyltransferase in tumors and cells of the oligodendrocyte lineage. *Canad J Neurol Sci* 22:111–115
2465. Obana WG, Cogen PH, Davis RL, Edwards MSB (1991) Metastatic juvenile pilocytic astrocytoma. *J Neurosurg* 75:972–975
2466. Oberc-Greenwood MA, McKeever PE, Kornblith PL, Smith BH (1984) A human ganglioglioma containing paired helical filaments. *Hum Pathol* 15:834–838
2467. Oberhaensli RD, Hilton-Jones D, Borne PJ, Hands LJ, Rampling RP, Radda GK (1986) Biochemical investigation of human tumours in vivo with phosphorus-31 magnetic resonance spectroscopy. *Lancet* 2(8497):8–11
2468. Oberling C (1922) Les tumeurs des méninges. *Bull Assoc Fr Cancer* 11:365–384
2469. Obermann B (1964) Intracranial teratoma replacing brain. Report of a case. *Arch Neurol* 11:423–426
2470. Obrador S, Lamas E (1956) Epidermoides intracraneales. (Tumores perlados). *Acta Neurochir (Wien)* 8:424–432
2471. Occhiogrosso M, Spada A, Merlicco G, Vailati G, DeBenedictis G (1985) Malignant cerebellar astrocytomas. Report of 5 cases. *J Neurosurg Sci* 29:43–50
2472. Odake G (1989) Intracranial hypoglossal neurinoma with extracranial extension: review and case report. *Neurosurgery* 24:583–587
2473. Oeckler R, Feiden W (1991) Benign symptomatic lesions of the pineal gland. Report of seven cases treated surgically. *Acta Neurochir (Wien)* 108:40–44
2474. Offit K, LoCoco F, Louie D, Parsa N, Leung D, Portlock C, Ye B, Lista F, Filippa D, Rosenbaum A, Ladanyi M, Jhanwar S, Dalla-Favera R, Chaganti R (1994) Rearrangement of the bcl-6 gene as a prognostic marker in diffuse large-cell lymphoma. *N Engl J Med* 331:74–80
2475. Ogasawara N (1965) The so-called "Rosenthal's fibers": their origin and histochemistry. *Clin Neurol* 5:65–71
2476. Ogawa K (1989) Embryonal neuroepithelial tumors induced by human adenovirus type 12 in rodents. 1. Tumor induction in the peripheral nervous system. *Acta Neuropathol (Berl)* 77:244–253
2477. Ogawa K, Oguchi M, Nakashima Y, Yamabe H (1989) Distribution of collagen type IV in brain tumors: an immunohistochemical study. *J Neurooncol* 7:357–366
2478. Ogawa T, Uemura K, Shisido F (1988) Changes of cerebral blood flow and oxygen and glucose metabolism following radiochemotherapy of gliomas: a PET study. *J Comput Assist Tomogr* 12:290–297
2479. Ohgaki H, Eibl RH, Wiestler OD, Yasargil MG, Newcomb EW, Kleihues P (1991) p53 mutations in nonastrocytic human brain tumors. *Cancer Res* 51:6202–6205
2480. Ohgaki E, Eibl RH, Schwab M, Reichel MB, Mariani L, Gehring M, Persen I, Höll T, Wiestler OD, Kleihues P (1993) Mutations of p53 tumor suppressor gene in neoplasms of the human nervous system. *Mol Carcinog* 8:74–80
2481. Ohnishi T, Sher PB, Posner JB, Shapiro WR (1990) Capillary permeability factor secreted by malignant brain tumor. Role on peritumoral brain edema and possible mechanism for anti-edema effect of glucocorticoids. *J Neurosurg* 72:245–251
2482. Oi S, Kokunai T, Matsumoto S (1990) Congenital brain tumors in Japan (ISPN Cooperative Study): specific clinical features in neonates. *Childs Nerv Syst* 6:86–91

2483. Oi S, Matsumoto S, Choi JU, Kang JK, Wuong T, Wang C, Chan TST (1990) Brain tumors diagnosed in the first year of life in 5 Far-Eastern Countries. Statistical analysis of 307 cases. *Childs Nerv Syst* 6:79–85
2484. Ojeda VJ, Spagnolo DV, Vaughan RJ (1987) Palisades in primary cerebral neuroblastoma simulating so-called polar spongioblastoma: a light and electron microscopical study of adult case. *Am J Surg Pathol* 11:316–322
2485. Oka K, Hirakawa K, Yoshida S (1989) Primary calvarial meningiomas. *Surg Neurol* 32:304–310
2486. Okeda R, Mochizuchi T, Terao E, Matsutani M (1980) The origin of intracranial fibrosarcoma. *Acta Neuropathol (Berl)* 52:223–230
2487. Okuda Y, Taomoto K, Saya H, Tjichi A, Kokunai T, Tamaki N, Matsumoto S (1988) Pineoblastoma with neuronal differentiation. Immunohistochemical and immunocytochemical studies. *J Neurooncol* 6:193–198
2488. Oldendorf WH, Cornford ME, Brown WJ (1977) The large apparent work capability of the blood barrier: a study of the mitochondrial content of capillary endothelial cells in brain and other tissues of the rat. *Ann Neurol* 1:409–417
2489. Oldfield EH, Friedman R, Kinsella T, Moquin R, Olson JJ, Orr K, DeLuca AM (1990) Reduction in radiation-induced brain injury by use of pentobarbital or lidocaine protection. *J Neurosurg* 72:737–744
2490. Olin GR, Ahlbom A (1980) The cancer mortality among Swedish chemists graduated during three decades. *Environ Res* 22:154–161
2491. Olin GR, Vagero D, Ahlbom A (1985) Mortality experience of electrical engineers. *Br J Ind Med* 42:211–212
2492. Oliner JD, Pietenpol JA, Thiagalingam S, Gyuris J, Kinzler KW, Vogelstein B (1993) Oncoprotein MDM2 conceals the activation domain of tumour suppressor p53. *Nature* 362:857–860
2493. Olivecrona H (1947) The parasagittal meningiomas. *J Neurosurg* 4:327–341
2494. Olivecrona H (1952) The cerebellar angiectolomas. *J Neurosurg* 9:317–330
2495. Olopade OI, Jenkins RB, Ransom DT, Malik K, Pomykala H, Nobori T, Cowan JM, Rowley JD, Diaz MO (1992) Molecular analysis of deletions of the short arm of chromosome 9 in human gliomas. *Cancer Res* 52:2523–2539
2496. Olsen KD (1994) Tumors and surgery of parapharyngeal space. *Laryngoscope* 104:1–28
2497. Olshan AF, Breslow NE, Daling JR (1986) Childhood brain tumors and paternal occupation in the aerospace industry. *J Natl Cancer Inst* 77:17–19
2498. Olson JJ, Beck DW, Schlechte JA, Loh P-M (1987) Effect of the antiprogesterone RU-38486 on meningioma implanted into nude mice. *J Neurosurg* 66:584–587
2499. Olson JJ, Friedman R, Orr K, Delaney R, Oldfield EH (1990) Cerebral radioprotection by pentobarbital: dose-response characteristics and association with GABA agonist activity. *J Neurosurg* 72:749–758
2500. Olson ME, Chernik NL, Posner JB (1974) Infiltration of the leptomeninges by systemic cancer. *Arch Neurol* 30:122–137
2501. Olszewski J (1964) Intramedullary neuromas of the spinal cord. *J Neuropathol Exp Neurol* 23:201 (discussion)
2502. Olvera-Rabiela JE, Altamirano-Dimas M, Cisneros Davila A (1971) Ependymoblastoma; informe de uno caso y revision de la literatura. *Pathologia* 9:27–33
2503. Onda K, Tanaka R, Takahashi H, Takeda N, Ikuta F (1989) Cerebral glioblastoma with cerebrospinal fluid dissemination: a clinicopathological study of 14 cases examined by complete autopsy. *Neurosurgery* 25:533–540
2504. Onda K, Davis RL, Wilson CB, Hoshino T (1994) Regional differences in bromodeoxyuridine uptake, expression of Ki-67 protein, and nucleolar organizer region counts in glioblastoma multiforme. *Acta Neuropathol (Berl)* 87:586–593
2505. Opalski A (1934) Studien zur allgemeinen Histopathologie der Ventrikelwände. *Z Gesamte Neurol Psychiatr* 150:42–47
2506. Oppenheimer DR (1955) A benign “tumor” of the cerebellum. Report of two cases of diffuse hypertrophy of the cerebellar cortex with review of nine previously reported cases. *J Neurol Neurosurg Psychiatry* 18:199–213
2507. Oppenheimer DR (1969) The effect of irradiation on a medulloblastoma. *J Neurol Neurosurg Psychiatry* 32:94–98

2508. Orchard G, Wilson Jones E. (1994) Immunocytochemistry in the diagnosis of malignant melanoma. *Br J Biomed Sci* 51:44–56
2509. Ordonez NG, Mackay B (1993) Neuroendocrine tumors of the nasal cavity. *Pathol Annu* 28:77–111
2510. Orian JM, Vasilopoulos K, Yoshida S, Kaye AH, Chow CW, Gonzales MF (1992) Overexpression of multiple oncogenes related to histological grade of astrocytic glioma. *Br J Cancer* 66:106–112
2511. Origitano TC, Karest SM, Hennkin RE (1993) Photodynamic therapy for intracranial neoplasms: investigations of photosensitizer uptake and distribution using indium-111 photofin-II single photon emission computed tomography scans in humans with intracranial neoplasms. *Neurosurgery* 32:357–364
2512. Orlidge A, D'Amore P (1986) Pericyte and smooth muscle cell modulation of endothelial cell proliferation. *J Cell Biol* 103 (5/2):471
2513. Osterberg KA, Watterberg LW (1962) Oxidative histochemistry of reactive astrocytes. *Arch Neurol* 7:211–218
2514. Ostertag B (1936) Einteilung und Charakteristic der Hirngewächse. Fischer, Jena
2515. Ostertag CB (1988) Reliability of stereotactic brain tumor biopsy. In: Lunsford LD (ed) *Modern Stereotactic Neurosurgery*. Nijhoff, Boston, pp 129–136
2516. Ostertag CB (1989) Stereotactic interstitial radiotherapy for gliomas. In: Broggi G, Gerosa MA (eds): *Cerebral gliomas*, Elsevier, Amsterdam, pp 207–215
2517. Ostertag CB, Warnke P, Kleihues P (1984) Iodine<sup>125</sup> interstitial irradiation of virally induced dog brain tumors. *Neurol Res* 6:176–180
2518. Ostertag CB, Volk B, Shibata T, Burger P, Kleihues P (1987) The monoclonal antibody Ki-67 as a marker for proliferating cells in stereotactic biopsies of brain tumours. *Acta Neurochir (Wien)* 89:117–121
2519. Ostor AG, Fortune DW (1978) Tuberos sclerosi initially seen as hydrops fetalis. Report of a case and review of the literature. *Arch Pathol Lab Med* 102:34–39
2520. Ovary E, Bencze Y (1966) Meningioma organization in tissue culture. *Proc V Intern Congr Neuropathol Zürich 1965 Exc Med Found*, p 916
2521. Oyasu R, Battifora HA, Clasen RA, McDonald JH, Hass GM (1970) Induction of cerebral gliomas in rats with dietary lead subacetate and 2-acetylaminofluorene. *Cancer Res* 30:1248–1261
2522. Paasivuo R, Saksela E (1983) Non-specific binding of mouse immunoglobulins by swollen-bodies astrocytes – a potential source of confusion in human brain immunohistochemistry. *Acta Neuropathol (Berl)* 59:103–108
2523. Packer RJ (1990) Chemotherapy for medulloblastoma/primitive neuroectodermal tumors of the posterior fossa. *Ann Neurol* 28:823–828
2524. Packer RJ, Sutton LN, Rosenstock JG, Rorke LB, Bilaniuk LT, Zimmermann RA, Littman PA, Bruce DA, Schut L (1984) Pineal region tumors of childhood. *Pediatrics* 74:97–102
2525. Packer RJ, Sutton LN, Rorke LB, Littman PA, Spoto R, Rosenstock JG, Bruce DA, Schut L (1984) Prognostic importance of cellular differentiation in medulloblastoma of childhood. *J Neurosurg* 61:296–301
2526. Packer RJ, Sutton LN, Rorke LB, Rosenstock JG, Zimmermann RA, Littman PA, Bilaniuk LT, Bruce DA, Schut L (1984) Intracranial embryonal cell carcinoma. *Cancer* 54:520–524
2527. Packer RJ, Siegel KR, Sutton LN, Littmann P, Bruce DA, Schut L (1985) Leptomeningeal dissemination of primary central nervous system tumors of childhood. *Ann Neurol* 18:217–221
2528. Packer RJ, Sutton LN, Rorke LB, Zimmerman RA, Littman P, Bruce DA, Schut L (1985) Oligodendroglioma of the posterior fossa in childhood. *Cancer* 56:195–199
2529. Packer RJ, Zimmerman R, Bilaniuk LT (1986) Magnetic resonance imaging in the evaluation of treatment related central nervous system damage. *Cancer* 58:635–640
2530. Packer RJ, Schut L, Siegel KR (1987) Dissemination of primary central nervous system tumors of childhood: incidence and clinical implications. *Prog Exp Tumor Res* 30:206–214
2531. Packer RJ, Sutton LN, Atkins TE, Radcliffe J, Bunin GR, D'Angio G, Siegel KR, Schut L (1989) A prospective study of cognitive function in children receiving whole-brain radiotherapy and chemotherapy: 2-year results. *J Neurosurg* 70:707–713
2532. Packer RJ, Sutton LN, Goldwein JW, Perilongo G, Bunin G, Ryan J, Cohen BH, D'Angio G, Kramer ED, Zimmerman RA, Rorke LB, Evans AE, Schut L (1991) Improved survival with

- the use of adjuvant chemotherapy in the treatment of medulloblastoma. *J Neurosurg* 74:433–440
2533. Packer RJ, Perilongo G, Johnson D, Sutton LN, Vezina G, Zimmerman RA, Ryan J, Reaman G, Schut L (1992) Choroid plexus carcinoma of childhood. *Cancer* 69:580–585
2534. Padgett BL, Walker DL, Zu Rhein GM, Varakis N (1977) Differential neurooncogenicity of strains of JC virus, a human poliovirus, in newborn Syrian hamsters. *Cancer Res* 37:718–720
2535. Paetau A, Virtanen I, Stenman S, Kurki P, Linder E, Vaheri A, Westermarck B, Dahl D, Haltia M (1979) Glial fibrillary acidic protein and intermediate filaments in human glioma cells. *Acta Neuropathol (Berl)* 47:71–74
2536. Paganetti PA, Caroni P, Schwab ME (1988) Glioblastoma infiltration into central nervous system tissue in vitro: involvement of a metalloprotease. *J Cell Biol* 107:2281–2291
2537. Page RB, Plourde PV, Coldwell D, Heald JL, Weinstein J (1983) Intracellular mixed germ cell tumor. *J Neurosurg* 58:766–770
2538. Paggi MG, Carapella CM, Fanciulli M (1988) Effect of lonidamine on human malignant gliomas: biochemical studies. *J Neurooncol* 6:203–209
2539. Pagni CA, Faccani G, Lanotte M (1991) I tumori primitivi del midollo spinale. Minerva Medica, Torino
2540. Paillass JE, Bonnal J, Legré J, Combalbert A (1961) Des méningiomes multiples à la méningiome en plaques au cours de la maladie de Recklinghausen. *Presse Med* 56:2604–2606
2541. Paillass JE, Combalbert A, Berard-Badier M, Bille J, Frank R (1964) Etude sur l'évolution des oligodendrogliomes de l'encéphale. A propos d'une série opératoire de 34 cas. *Acta Neurol Psych Belg* 64:537–551
2542. Paine JT, Handa H, Yamasaki T, Yamashita J, Miyatake S (1986) Immunohistochemical analysis of infiltrating lymphocytes in central nervous system tumors. *Neurosurgery* 18:766–772
2543. Pallis CA, Louis S, Morgan RL (1961) Radiation myelopathy. *Brain* 84:460–479
2544. Palma L, Guidetti B (1985) Cystic pilocytic astrocytomas of the cerebral hemispheres. Surgical experience with 51 cases and long-term results. *J Neurosurg* 62:811–815
2545. Palma L, Di Lorenzo N, Guidetti B (1978) Lymphocytic infiltrates in primary glioblastomas and recidivous gliomas: incidence, fate and relevance to prognosis in 228 operated cases. *J Neurosurg* 49:854–861
2546. Palma L, Maleci A, Di Lorenzo N, Lauro G (1985) Pleomorphic xanthoastrocytoma with 18-year survival. Case report. *J Neurosurg* 63:808–810
2547. Palma L, Vagnozzi R, Annino I, Chiappetta P, Maleci A, Cantore GP (1988) Post-radiation glioma in a child: case report and review of the literature. *Childs Nerv Syst* 4:296–301
2548. Palma L, Celli P, Cantore G (1993) Supratentorial ependymomas of the first two decades of life. Long-term follow-up of 20 cases (including two subependymomas). *Neurosurgery* 32:169–175
2549. Palmer JJ (1972) Radiation myelopathy. *Brain* 95:109–122
2550. Palmer JO, Kasselberg AG, Netsky MG (1981) Differentiation of medulloblastoma. Studies including immunohistochemical localization of glial fibrillary acidic protein. *J Neurosurg* 55:161–169
2551. Pang D (1993) Surgical management of craniopharyngioma. In: Sekkar LN, Janecka IP (eds) *Surgery of cranial base tumors*. Raven, New York, pp. 787–807
2552. Pang D, Ashmead JW (1982) Extraneural metastasis of cerebellar glioblastoma multiforme. *Neurosurgery* 10:252–257
2553. Paoletti P, Butti G (1987) Therapy of malignant brain tumors. *Prog Clin Neurosurg* 1:69–76
2554. Paoletti P, Fumagalli R, Weiss JF, Pezzotta S (1977) Desmosterol: A biochemical marker of glioma growth. *Surg Neurol* 8:399–405
2555. Paoletti P, Butti G, Zibera C, Scerrati M, Gibelli N, Roselli R, Magrassi L, Sica G, Rossi G, Robustelli della Cuna G (1990) Characteristics and biological role of steroid hormone receptors in neuroepithelial tumors. *J Neurosurg* 73:736–742
2556. Pardatscher K, Iraci G, Cappellotto P, Rigobello L, Pellone M, Fiore D (1979) Multiple intramedullary neurinomas of the spinal cord. *J Neurosurg* 50:817–822
2557. Parent AD (1991) Multiple meningiomas. In: Al-Mefty O (ed) *Meningiomas*. Raven, New York, pp 161–168



2558. Parham DM, Weeks DA, Beckwith JB (1994) The clinicopathologic spectrum of putative extrarenal rhabdoid tumors. An analysis of 42 cases studied with immunohistochemistry or electron microscopy. *Am J Surg Pathol* 18:1010-1029
2559. Park TS, Hoffman HJ, Hendrick EB, Humphreys RP, Becker LE (1983) Medulloblastoma: clinical presentation and management: experience at the Hospital for Sick Children, Toronto, 1950-1980. *J Neurosurg* 58:543-552
2560. Parker C, Whittaker P, Weeks RJ, Thody AJ, Sherbert GV (1991) Modulators of metastatic behaviour alter the expression of metastasis-associated mts1 and nm23 genes in metastatic variants of the B16 murine melanoma. *Clin Biotech* 3:217-222
2561. Parker JC Jr, Mortara RH, McCloskey JJ (1975) Biological behavior of the primitive neuroectodermal tumors: significant supratentorial childhood gliomas. *Surg Neurol* 4:383-388
2562. Partington MD, Davies DM (1990) Radiation induced meningioma after treatment for pituitary adenoma: case report and literature review. *Neurosurgery* 26:329-331
2563. Paschen W, Hossmann KA, van den Kerckhoff W (1983) Regional assessment of energy-producing metabolism following prolonged complete ischemia of cat brain. *J Cereb Blood Flow Metab* 3:321-329
2564. Pasquier B, Couderc P, Pasquier D, Prinh MH, Arnould JP (1978) Sarcoma arising in oligodendroglioma of the brain: a case with intramedullary and subarachnoid spinal metastases. *Cancer* 42:2753-2758
2565. Pasquier B, Kojer I, Labat F, Keddari E, Pasquier D, Steebner P, Barge M, Delpech B, Conderc P (1985) Le xanthoastrocytome du sujet jeune: revue de la littérature à propos de deux observations d'évolution discordante. *Ann Pathol* 5:29-43
2566. Pasquier B, Gasnier F, Pasquier D, Keddari E, Morens A, Couderc P (1986) Papillary meningioma - clinicopathologic study of seven cases and review of the literature. *Cancer* 58:299-305
2567. Pastore G, Magnani C, Zanetti R (1981) Incidence of cancer in children in the province of Torino (Italy) 1967-1978. *Europ J Cancer Clin Oncol* 17:1337-1351
2568. Patchell, Tibbs PA, Walst JW, Dempsey RJ, Maruyama Y, Kryscia RY, Markesbery WR, MacDonald JS, Young B (1990) A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med* 322:494-500
2569. Patel JK, Didolkar MS, Pickren JW, Moore RH (1978) Metastatic pattern of malignant melanoma. *Am J Surg* 135:807-810
2570. Pator A, Petch CP (1954) Association of diabetes mellitus with cerebral tumour. *Br it Med J* 1:855-856
2571. Patrick BS, Smith RR, Bailey TO (1974) Aseptic meningitis due to spontaneous rupture of a craniopharyngioma cyst. Case report. *J Neurosurg* 41:387-390
2572. Patronas NJ, Di Chiro G, Kafta C (1985) Prediction of survival in glioma patients by means of positron emission tomography. *J Neurosurg* 62:816-822
2573. Pattengale PK, Taylor CR, Panke T, Tatter D, McCormick RA, Rawlinson DG, Davis RL (1979) Selective immunodeficiency and malignant lymphoma of the central nervous system. Possible relationship to Epstein-Barr virus. *Acta Neuropathol (Berl)* 48:165-169
2574. Paulus W, Jänisch W (1990) Clinicopathologic correlations in epithelial choroid plexus neoplasms: study of 52 cases. *Acta Neuropathol (Berlin)* 80:635-641
2575. Paulus W, Jellinger K (1992) Desmoplastic spindle-cell glioblastoma or gliosarcoma? *Neuropathol Appl Neurobiol* 18:207-208
2576. Paulus W, Jellinger K (1993) Comparison of integrin adhesion molecules expressed by primary brain lymphomas and nodal lymphomas. *Acta Neuropathol (Berl)* 86:360-364
2577. Paulus W, Peiffer J (1988) Does the pleomorphic xanthoastrocytoma exist? Problems in the application of immunological techniques to the classification of brain tumors. *Acta Neuropathol (Berl)* 76:245-252
2578. Paulus W, Peiffer J (1989) Intratumoral histologic heterogeneity of gliomas. A quantitative study. *Cancer* 64:442-447
2579. Paulus W, Roggendorf W, Schuppan D (1988) Immunohistochemical investigation of collagen subtypes in human glioblastoma. *Virchows Arch A Pathol Anat His* 413:325-332
2580. Paulus W, Peiffer J, Grote E (1989) Intracerebral malignant fibrous histiocytoma at site of a previously excised low grade glioma. *Acta Neurochir (Wien)* 99:161-165

2581. Paulus W, Peiffer J, Roggendorf W, Schuppan D (1989) Meningio-angiomatosis. *Pathol Res Pract* 184:446–452
2582. Paulus W, Jellinger K, Brenner H (1989) Melanotic paraganglioma of the orbit: a case report. *Acta Neuropathol (Berl)* 79:340–346
2583. Paulus W, Grothe C, Sensenbrenner M, Janet T, Baur I, Graf M, Roggendorf W (1990) Localization of basic fibroblastic growth factor, a mitogen and angiogenic factor, in human brain tumors. *Acta Neuropathol (Berl)* 79:418–423
2584. Paulus W, Slowik F, Jellinger K (1991) Primary intracranial sarcomas: histopathologic features of 19 cases. *Histopathol* 17: 18:395–402
2585. Paulus W, Schlote W, Perentes E, Jacobi G, Warmuth-Metz M, Roggendorf W (1992) Desmoplastic supratentorial neuroepithelial tumours of infancy. *Histopathology* 21:43–49
2586. Paulus W, Jellinger K, Hallas C, Ott G, Muller-Hermelink H (1993) Human herpesvirus-6 and Epstein-Barr virus genome in primary cerebral lymphomas. *Neurology* 43:1591–1593
2587. Paulus W, Lisle DK, Tonn JC, Wolf HK, Reggendorf W, Revves S, Louis DN (1996) Molecular genetic alterations in pleomorphic xanthoastrocytoma. *Acta Neuropathol (Berl)* 91:293–297
2588. Paxton HD (1959) Quantitative histochemistry of brain tumors and analogous normal tissue. *Neurology* 9:367–370
2589. Peach M (1977) Renin-angiotensin system. *Physiol Rev* 57:313–370
2590. Pearl GS, Takei Y (1981) Cerebellar “neuroblastoma”: nosology as it relates to medulloblastoma. *Cancer* 47:772–779
2591. Pearl GS, Takei Y, Stefanis GS Hoffman JC (1981) Intraventricular neuroblastoma in a patient with Von-Hippel-Lindau’s disease. Light and electron microscopic study. *Acta Neuropathol (Berl)* 53:253–256
2592. Pearse AGE (1969) The cytochemistry and ultrastructure of polypeptide hormone-producing cells of APUD series and the embryologic, physiologic and pathologic implications of the concept. *J Histochem Cytochem* 17:303–313
2593. Pearson J, Milstoc M, Harris J, Budzilovich GN, Feigin I (1976) Anaplastic neuronal tumors of brain. *Cancer* 38:1424–1437
2594. Pedersen PL (1978) Tumor mitochondria and the bioenergetics of cancer cells. *Progr Exp Tumor Res* 22:190–274
2595. Pegg AE (1995) Inactivation of 0<sup>6</sup>-alkylguanine-DNA alkyltransferase as a means to enhance the effectiveness of chloroethylating and methylating agents. Proceedings of the 11<sup>th</sup> International Conference on Brain Tumor Research and Therapy, 31 October–3 November, Silverado, Ca
2596. Pelc S, Brihaye J, Périer O, Heimann R, Baleriaux D (1977) Temporal lobe oligodendroglioma developing from infancy into adulthood. *Ann Neurol* 2:537–540
2597. Pelfrene AF, Love LA (1977) Experimental induction of melanotic tumors in Syrian golden hamsters by transplacental and topical application of ethylnitrosourea. *Krebsforsch Klin Onkol* 30:233–239
2598. Pellat J, Perret J, Pasquier B, Hommel M, Vinard JL, Pollak P (1980) Lésions post-radiothérapiques tardives des artères cervicales à destinée cérébral. *Rev Neurol (Paris)* 2:147–163
2599. Pendergrass TW, Milstein JM, Geyer JR, Mulne FA, Kosnik EJ, Monis JD, Heideman RL, Ruyman FB, Stuntz JT, Bleyer WA (1987) Eight-drugs-in-one day chemotherapy for brain tumors: experience in 107 children and rationale for preradiation chemotherapy. *J Clin Oncol* 5:1221–1231
2600. Penfield W (1927) Principles of the pathology of neurosurgery. In: Loose-leaf surgery. Nelson and Sons, New York, pp 303–347
2601. Penfield W (1927) The encapsulated tumors of the nervous system. *Surg Gynec Obstet* 45:178–190
2602. Penfield W (1932) Cytology and cellular pathology of the nervous system. Hoeber, New York
2603. Penfield W (1932) Tumors of the sheaths of the nervous system. In: Penfield’s cytology and cellular pathology of the nervous system, vol 3. Hoeber, New York, pp 953–990
2604. Penfield W, Ward A (1948) Calcifying epileptogenic lesions (emangioma calcificans). *J Neuropathol Exp Neurol* 7:111
2605. Penn I (1981) Malignant lymphoma in organ transplant recipients. *Transplant Proc* 13:736–738

2606. Pennybacker J (1954) Recurrence in cerebellar haemangiomas. *Zbl Neurochir* 14:63–73
2607. Peña CE (1975) Intracranial hemangiopericytoma. Ultrastructural evidence of its leiomyoblastic differentiation. *Acta Neuropathol (Berl)* 33:279–284
2608. Perantoni A, Rice JM, Reed CD, Watatani M, Wenk ML (1987) Activated neu oncogenes sequences in primary tumors of the nervous system induced in rats by transplacental exposure to ethylnitrosourea. *Proc Natl Acad Sci (USA)* 84:6317–6321
2609. Percy AK, Elveback LR, Okazaky H, Kurland LT (1972) Neoplasms of the nervous system: epidemiologic considerations. *Neurology* 22:40–48
2610. Perentes E (1990) Retinal S-antigen immunoreactivity in pineal parenchymal tumors and medulloblastomas. Symposium on Brain Tumor Pathology, 9–10 September, Biwako, Japan, pp 25
2611. Perentes E, Rubinstein LJ (1985) Immunohistochemical recognition of human nerve sheath tumors by anti-Leu 7 (HNK-1) monoclonal antibody. *Acta Neuropathol (Berl)* 68:319–324
2612. Perentes E, Rubinstein LJ (1986) Non-specific binding of mouse myeloma IgM immunoglobulins by human myelin sheath and astrocytes. *Acta Neuropathol (Berl)* 70:284–288
2613. Perentes E, Rubinstein LJ (1986) Immunohistochemical recognition of human neuroepithelial tumors by anti-Leu-7 (HNK-1) monoclonal antibody. *Acta Neuropathol (Berl)* 69:227–233
2614. Perentes E, Rubinstein LJ (1987) Recent applications of immunoperoxidase histochemistry in human neuro-oncology. *Arch Pathol Lab Med* 111:796–812
2615. Perentes E, Rubinstein LJ, Herman MM, Donoso LA (1986) S-antigen immunoreactivity in human pineal glands and pineal parenchymal tumors. A monoclonal antibody study. *Acta Neuropathol (Berl)* 71:224–227
2616. Perentes E, Hebert CP, Rubinstein LJ, Herman MM, Uffer S, Donoso LA, Collins VP (1987) Immunohistochemical characterization of human retinoblastomas in situ with multiple markers. *Am J Ophthalmol* 103:647–658
2617. Perria C, Carai M, Falzoi A, Orunesu G, Rocca A, Massarelli G, Francaviglia M, Jori G (1988) Photodynamic therapy of malignant tumours: clinical results of difficulties with and future prospects for the neurosurgical application. *Neurosurgery* 23:557–563
2618. Perry JR, Ang LC, Bilbao JM, Muller PJ (1995) Clinicopathologic features of primary and postirradiation cerebral gliosarcoma. *Cancer* 75:2910–2918
2619. Pershose MA, Stubblefield E, Hadi A, Killary AM, Yung WKA, Steck PA (1993) Analysis of the functional role of chromosome 10 loss in human glioblastomas. *Cancer Res* 53:5043–5050
2620. Peters A, Feldman M (1973) The cortical plate and the molecular layer of the late rat fetus. *Z Anat Entwicklungsgesch* 141:3–37
2621. Peters A, Palay SL, Webster HdeF (1970) The fine structure of the nervous system. The cells and their processes. Hoeber–Harper and Row, New York
2622. Peters A, Palay SL, Webster HdeF (1976) The fine structure of the nervous system; the neurons and supporting cells. Saunders, Philadelphia
2623. Peters G (1952) Hirntrauma und Glioma. *Fortschr Neurol Psychiat* 20:403–422
2624. Peters G (1955) Patologia del sistema nervoso. Sansoni, Firenze
2625. Peters JB, Preston-Martin S, Yu MC (1981) Brain tumors in children and occupational exposure of parents. *Science* 213:235–237
2626. Peterson K, Paleologos N, Forsyth P, MacDonald DR, Cairncross JG (1995) Salvage chemotherapy for recurrent malignant oligodendrogliomas. *Proc Am Soc Clin Oncol* 14:149–155
2627. Petito CK, De Girolami U, Earle KM (1976) Craniopharyngiomas. A clinical and pathological review. *Cancer* 37:1944–1952
2628. Pettinato G, De Chiara A, Insabato L, Ferbo U, Di Blasi A, Marsilia GM (1989) Reactive glioma in intracranial sarcoma (“sarcoglioma”) *Appl Pathol* 7:192–220
2629. Peyrard M, Fransson I, Xie YG, Han FY, Rutledge MH, Swahn S, Collins JE, Dunham I, Collins VP, Dumanski JP (1994) Characterization of a new member of the human beta-adaptin gene family from chromosome 22q12, a candidate meningioma gene. *Hum Molec Genet* 3:1393–1399
2630. Pflüger H, Schürmann P (1931) Die Histogenese ektomesodermaler Mischgeschwülste der Mundhöhle. Leipzig, George Thieme
2631. Philippon J, Cornu P (1991) The recurrence of meningiomas. In: Al-Mefty O (ed) *Meningiomas*. Raven, New York, pp 87–105
2632. Phillips MH, Stelzer KJ, Griffin TW, Mayberg MR, Winn HR (1994) Stereotactic radiosurgery: a review and comparison of methods. *J Clin Oncol* 12:1085–1099

2633. Phillips PC, Delattre JY, Berger CA, Rottenberg DA (1987) Early and progressive increase in regional brain capillary permeability following single and fractionated cranial irradiation in the rat. *Neurology* 37:301
2634. Phillips TL (1981) Sensitizers and protectors in clinical oncology. *Semin Oncol* 8:65–82
2635. Phillips TL, Chu WT (1995) Changing potential for neutron capture therapy in the treatment of CMS malignancy. *Proc 11th International Conference on Brain Tumor Research and Therapy*, 31 October–3 November, Silverado, Ca
2636. Pick L, Bielschowsky M (1911) Über das System der Neurone und Beobachtungen an einem Ganglioneurom des Gehirns nebst Untersuchung über die Genese der Nervenfasern in Neuronen. *Z Neurol* 6:391–437
2637. Piepmeier JM (1987) Observations on the current treatment of low-grade astrocytic tumors of the cerebral hemispheres. *J Neurosurg* 67:177–181
2638. Pierre-Kahn A, Hirsch JF, Roux FX, Renier D, Sainte-Rose C (1983) Intracranial ependymomas in childhood: survival and functional results in 47 cases. *Childs Brain* 10:145–156
2639. Pierre-Kahn A, Lacombe J, Pichon J, Giudicelli Y, Renier D, Sainte-Rose C, Perrigot M, Hirsch J-F (1986) Interspinal lipomas with spina bifida: prognosis and treatment in 73 cases. *J Neurosurg* 65:756–761
2640. Pigott TJ, Robson DK, Palmer J, Ward LM (1993) Expression of epidermal growth factor receptor in human glioblastoma multiforme. *Br J Neurosurg* 7:261–265
2641. Piguet V, Carrel S, Diserens AC, Mach JP, De Tribolet N (1986) Heterogeneity of the induction of HLA-DR expression by IFN Gamma on glioma cell lines and their clones. *J Natl Cancer Inst* 76:223–227
2642. Pilkington GJ (1992) Glioma heterogeneity in vitro: the significance of growth factors and gangliosides. *Neuropathol Appl Neurobiol* 18:434–442
2643. Pilkington GJ, Lantos PL (1982) The role of glutamine synthetase in the diagnosis of cerebral tumours. *Neuropathol Appl Neurobiol* 8:227–236
2644. Pilkington GJ, Lantos PL, Darling JC, Thomas DGT (1982) Three cell lines from a spontaneous murine astrocytoma show variation in astrocytic differentiation. *Neurosci Lett* 34:315–320
2645. Pilkington GJ, Darling JL, Lantos PL, Thomas DGT (1985) Tumorigenicity of cell lines (VMDK) derived from a spontaneous murine astrocytoma. Histology, fine structure and immunocytochemistry of tumours. *J Neurol Sci* 71:145–164
2646. Pilkington GJ, Martin K, Merzak A, Hatva VE, Rogers JP, Roxanis Y, Koocheckpour S (1993) Gangliosides and glioma cell motility. *J Neurooncol [Suppl]* 15:20
2647. Pisco K, Hoffmann G (1961) Das primäre melanoblastom des Zentralnervensystems. *Neurochirurgia* 4:1–26
2648. Pisco K, Stein F (1961) Glomus jugulare- (tympanicum)-Tumor. Klinische und pathologisch-anatomische Mitteilung. *Dtsch Ztschr Nervenheilk* 183:105–121
2649. Pitman SW, Frei E (1977) Weekly methotrexate-calcium leucovorin rescue; effect of alkalization on nephrotoxicity; pharmacokinetics in the CNS; and use in CNS non-Hodgkin's lymphoma. *Cancer Treat Rep* 61:695–701
2650. Pitt FW, Riggs HE (1964) Intramedullary neuromas of the spinal cord. *J Neuropathol Exp Neurol* 23:200
2651. Pixley SK, de Vellis J (1984) Transition between immature radial glia and mature astrocytes studied with a monoclonal antibody to vimentin. *Dev Brain Res* 15:201–209
2652. Pizzo PA, Miser JS, Cassady JR, Filler RM (1985) Solid tumors of childhood. In: De Vita VT, Helman S, Rosemberg S (eds) *Principles and practice of oncology*. Lippincott, Philadelphia, pp 1555–1563
2653. Plate KH, Breier G, Risau W (1994) Molecular mechanisms of developmental and tumor angiogenesis. *Brain Pathol* 4:207–218
2654. Plate KH, Breier G, Weich HA, Risau W (1992) Vascular endothelial growth factor is a potential tumour angiogenesis factor in human gliomas in vivo. *Nature* 359:845–848
2655. Plate KH, Rüschoff J, Behuke J, Mennel HD (1990) Proliferative potential of human brain tumours as assessed by nucleolar organizer regions (AgNORs) and KI-67-immunoreactivity. *Acta Neurochir (Wien)* 104:103–109

2656. Poisson M, Magdelenat H, Foncin JF, Bleibel JM, Philippon J, Pertuiset B, Buge A (1980) Récepteurs d'oestrogènes et de progestérone dans les méningiomes. Etude de 22 cas. *Rev Neurol* 136:193–203
2657. Poisson M, Pertuiset BF, Hauw JJ, Philippon J, Buge A, Mognilewsky M, Philibert D (1983) Steroid hormone receptors in human meningiomas, gliomas and brain metastases. *J Neurooncol* 1:179–189
2658. Pollack IF, Lunsford LD, Fliekinger JC, Dameshek HL (1989) Prognostic factors in the diagnosis and treatment of primary central nervous system lymphoma. *Cancer* 63:939–947
2659. Pollak A, Friede RL (1977) Fine structure of medulloepithelioma. *J Neuropathol Exp Neurol* 36:712–725
2660. Pollak IF, Gerszten PC, Martinez AJ, Lo K-H, Shulz B, Albright AL, Janosky J, Deutsch M (1995) Intracranial ependymomas of childhood: long-term outcome and prognostic factors. *Neurosurgery* 37:655–667
2661. Pollay M, Roberts A (1980) Blood-brain barrier: a definition of normal and altered function. *Neurosurgery* 6:675–685
2662. Polmeter FE, Kernohan JW (1947) Meningeal gliomatosis: study of 42 cases. *Arch Neurol Psychiatr* 57:593–616
2663. Pomerat CM (1955) Dynamic neuropathology. *J Neuropathol Exp Neurol* 14:28–38
2664. Pomerat CM, Todd EM, Goldblatt D (1962) Activity of meningioma whorls in vitro. In: Fields WS, Sharkey PC (eds) *The biology and treatment of intracranial tumors*. Thomas, Springfield, pp 102–121
2665. Pompili A, Calvase F, Caroli F, Mastrostefano R, Occhipinti E, Rans L, Sciarretta F (1993) The transdural extension of gliomas. *J Neurooncol* 15:67–74
2666. Pontén J (1975) Neoplastic human glia cells in vitro. Plenum, New York, pp 175–206
2667. Popoff NA, Ellsworth RM (1969) The fine structure of nuclear alterations in retinoblastoma and in the developing human retina: in vivo and in vitro observations. *J Ultrastruct Res* 29:535–549
2668. Popoff NA, Malinin TI, Rosomoff HC (1974) Fine structure of intracranial hemangiopericytoma and angiomatous meningioma. *Cancer* 34:1187–1197
2669. Poppen JL (1962) Surgical treatment of extracerebral intracranial tumors. In: Fields WS, Sharkey PC (eds) *The biology and treatment of intracranial tumors*. Thomas, Springfield, pp 457–480
2670. Porter PL, Gown AM, Kramp SG, Coltrera MD (1992) Widespread p53 overexpression in human malignant tumors. *Am J Pathol* 140:145–152
2671. Posey LC (1942) Papilloma of the choroid plexus. Report of a case and summary of recorded cases. *Arch Pathol* 34:911–916
2672. Posner JB (1980) Brain metastases: a clinician's view. In: Weiss L, Gilbert HA, Posner JB (eds) *Brain metastases*. Nijhoff, Boston, pp 2–29
2673. Posner JB (1992) Management of brain metastases. *Rev Neurol* 148:477–487
2674. Posner JB, Chernik NL (1978) Intracranial metastases from systemic cancer. *Adv Neurol* 19:579–592
2675. Povlishock JT, Becker DP, Sullivan HG, Miller JD (1978) Vascular permeability alterations to horse radish peroxidase in experimental brain injury. *Brain Res* 153:223–239
2676. Pradat PF, Poisson M, Delattre JY (1994) Post-radiation neuropathies: Experimental and clinical data. *Rev Neurol* 150:664–677
2677. Prados M, Leibel S, Barnett CM, Gutin P (1989) Interstitial brachytherapy for metastatic brain tumors. *Cancer* 63:657–660
2678. Prados MD, Schold C, Berger MS, Fulton D, Gilbert M, Kuhn J, Macdonald D, Metha M, Cairncross JG, Spence A, Chang S (1995) Clinical trial of the North American Brain Tumor Consortium (1995). In: 11th International Conference of Brain Tumor Research and Therapy, 31 October–3 November, Silverado, Ca (abstr)
2679. Prados MD, Warnick RE, Wara WM, Larson DA, Lamborn K, Wilson CB (1995) Medulloblastoma in adults. *Int J Radiat Oncol Biol Phys* 4:1145–1152
2680. Prayson RA, Estes ML (1992) Dysembryoplastic neuroepithelial tumor. *Am J Clin Pathol* 97:398–401

2681. Prayson RA, Khajavi K, Comair YG (1995) Cortical architectural abnormalities and MIB1 immunoreactivity in gangliogliomas: a study of 60 patients with intracranial tumors. *J Neuropathol Exp Neurol* 54:513–520
2682. Preston-Martin S (1985) The epidemiology of primary nervous system tumors in children. *Ital J Neurol Sci* 6:403–409
2683. Preston-Martin S, Paganini-Hill A, Henderson BE, Pike MC, Wood C (1980) Case-control study of intracranial meningiomas in women in Los Angeles county, California. *J Natl Cancer Inst* 65:67–73
2684. Preston-Martin S, Yu MC, Benton B, Henderson BE (1982) N-nitroso compounds and childhood brain tumors: a case-control study. *Cancer Res* 42:5240–5245
2685. Preston-Martin S, Henderson BE, Peters J (1982) Descriptive epidemiology of the central nervous system neoplasms in Los Angeles county. *Ann NY Acad Sci* 381:202–208
2686. Preston-Martin S, Yu MC, Henderson BE, Roberts C (1983) Risk factors for meningiomas in men in Los Angeles county. *J Natl Cancer Inst* 70:863–866
2687. Preston-Martin S, Mack W, Henderson BE (1989) Risk factors for gliomas and meningiomas in male in Los Angeles county. *Cancer Res* 49:6137–6143
2688. Price M, Lazzaro D, Pohl T, Mattei M-G, Rüther U, Olivo J-C, Duboule D, Di Lauro R (1992) Regional expression of the homeobox gene *Nkx-2.2* in the developing mammalian forebrain. *Neuron* 8:241–255
2689. Price RA, Birdwell DA (1978) The central nervous system in childhood leukemia. III. Mineralizing microangiopathy and dystrophic calcification. *Cancer* 42:717–728
2690. Price RA, Lee PA, Albright AL, Ronneklin OF, Gutai JP (1984) Treatment of sexual precocity by removal of a luteinizing hormone-releasing hormone secreting hamartoma. *JAMA* 251:2247–2249
2691. Prichard RV, Custer RP (1952) Pacinian neurofibroma. *Cancer* 5:297–309
2692. Prince FP (1981) Ultrastructural aspects of myogenesis found in neoplasms. *Acta Neuropathol (Berl)* 54:315–320
2693. Pringle N, Collarini EJ, Mosley MJ, Heldin C-H, Westermarck B, Richardson WD (1989) PDGF A chain homodimers drive proliferation of bipotential (0–2A) glial progenitor cells in the developing rat optic nerve. *EMBO J* 8:1049–1056
2694. Pringle NP, Richardson WD (1993) A singularity of PDGF alpha receptor expression in the dorsoventral axis of the neural tube may define the origin of the oligodendrocyte lineage. *Development* 117:525–533
2695. Pritchett PS, King TT (1978) Dysplastic gangliocytoma of the cerebellum. An ultrastructural study. *Acta Neuropathol (Berl)* 42:1–5
2696. Pruss RM, Mirsky R, Raff MC (1981) All classes of intermediate filaments share a common antigenic determinant defined by a monoclonal antibody. *Cell* 27:419–428
2697. Puchtler H, Meloan SN (1985) On the chemistry of formaldehyde fixation and its effects on immunohistochemical reactions. *Histochemistry* 82:201–204
2698. Puelles L, Rubenstein R (1993) Expression patterns of homeobox and other putative regulatory genes in the embryonic mouse forebrain suggest a neuromeric organization. *TINS* 11:472–479
2699. Queiroz LS, Lopes de Faria J, Cruz Neto JN (1975) An ependymoblastoma of the pons. *J Pathol* 115:207–210
2700. Quigley MR, Maroon J (1991) The relationship between survival and the extent of the resection in patients with supratentorial malignant gliomas. *Neurosurgery* 29:285–389
2701. Raaphorst GP, Feeley MM, Da Silva VF, Danjoux CE, Gerig LH (1989) A comparison of heat and radiation sensitivity of three human glioma cell lines. *Int J Radiat Oncol Biol Phys* 17:615–622
2702. Radlakrishnan K, Mokri B, Parisi JE, O'Fallow WM, Sunku J, Kurland LT (1995) The trends in incidence of primary brain tumors in the population of Rochester, Minnesota. *Ann Neurol* 37:67–73
2703. Raff MC (1989) Glial cell diversification in the rat optic nerve. *Science* 243:1450–1455
2704. Raff MC, Fields KL, Hakamori S-I, Mirsky R, Pruss RM, Winter J (1979) Cell-type specific markers for distinguishing and studying neurons and the mayor classes of glial cells in culture. *Brain Res* 174:283–308

2705. Raff MC, Miller RH, Noble M (1983) A glial progenitor cell that develops in vitro into an astrocyte or an oligodendrocyte depending on culture medium. *Nature*, 303:390–396
2706. Raff MC, Abney ER, Miller RH (1984) Two glial cell lineages diverge prenatally in rat optic nerve. *Dev Biol* 106:53–60
2707. Raff MC, Lillien LE, Richardson WD, Burne JF, Noble M (1988) Platelet-derived growth factor from astrocytes drives the clock that times oligodendrocyte development in culture. *Nature* 333:562–565
2708. Raffel C, Edwards MSB, Davis RL, Alhin AR (1985) Postirradiation cerebellar glioma. *J Neurosurg* 62:300–303
2709. Raffel C, Gilles FE, Weinberg KI (1990) Reduction of homozygosity and gene amplification in central nervous system primitive neuroectodermal tumors of childhood. *Cancer Res* 50:587–591
2710. Raffel C, Thomas GA, Tishler DM, Lassoff S, Allen JC (1993) Absence of p53 mutations in childhood central nervous system primitive neuroectodermal tumors. *Neurosurgery* 33:301–305
2711. Raghavan R, Steart PV, Weller RO (1990) Cell proliferation patterns in the diagnosis of astrocytomas, anaplastic astrocytomas and glioblastoma multiforme: a Ki-67 study. *Neuropathol Appl Neurobiol* 16:123–133
2712. Raimondi AJ (1993) Craniopharyngioma: complications and treatment failures. Weaken case for aggressive surgery. *Crit Rev Neurosurg* 3:7–24
2713. Raimondi AJ, Tomita T (1979) Medulloblastoma in childhood. *Childs Brain* 5:310–328
2714. Raimondi AJ, Tomita T (1983) Brain tumors during the first year of life. *Childs Brain* 10:193–207
2715. Raimondi AJ, Mullan S, Evans JP (1962) Human brain tumors: an electron microscopic study. *J Neurosurg* 19:731–753
2716. Rajewski MF (1982) Pulse-carcinogenesis by ethylnitrosourea in the developing rat nervous system: molecular and cellular mechanisms. In: Nicolin A (ed) *Chemical carcinogenesis*. Plenum, New York, pp 363–379
2717. Raju T, Adelman LS, Dahl O, Bignami A (1983) Localization of keratin in the notochord and in notochord derived tumors – immunohistological study of rat embryo and human chordoma. *Int J Dev Neurosci* 1:375–384
2718. Rakic P (1971) Guidance of neurons migrating to the foetal monkey neocortex. *Brain Res* 33:471–467
2719. Rakic P (1971) Neuron-glia relationship during granule cell migration in developing cerebellar cortex. A Golgi and electron microscopic study in macacus rhesus. *J Comp Neurol* 141:283–312
2720. Rakic P (1972) Mode of cell migration to the superficial layers of foetal monkey neocortex. *J Comp Neurol* 145:61–84
2721. Rakic P (1977) Genesis of the dorsal lateral geniculate nucleus in the Rhesus monkey: site and time of origin, kinetics of proliferation, routes of migration and patterns of distribution of neurons. *J Comp Neurol* 176:23–52
2722. Rakic P, Sidman RL (1968) Sub-commissural organ and adjacent ependyma: autoradiographic study of their origin in the mouse brain. *Amer J Anat* 122:317–336
2723. Ramaekers FCS, Puts JJG, Kant A, Moesker O, Jap PHK, Vooijs GP (1983) Antibodies to intermediate filaments as a tool in tumor diagnosis. *Cell Biol Int Rep* 6:652–654
2724. Ramamurthi B, Anguli VC, Iyer CGS (1958) A case of intramedullary neurinoma. *J Neurol Neurosurg Psychiatry* 21:92–94
2725. Ramamurthi B, Iyer CGS, Vedachalam SP (1961) Intracranial meningeal chondroma. *J Neurosurg* 18:826–828
2726. Ramsey HJ (1965) Fine structure of the surface of the cerebral cortex of human brain. *J Cell Biol* 26:323–333
2727. Rana MW, Pinkerton H, Thornton H, Nagy D (1977) Heterotransplantation of human glioblastoma multiforme and meningioma to nude mice. *Proc Soc Exp Biol Med* 155:85–88
2728. Raney RB, Courville CB (1937) Multiple hemangioblastomas of the central nervous system. *Bull Los Angeles Neurol Soc* 2:104–114

2729. Ransom DT, Ritland SR, Kimmel DW, Moertel CA, Dahl RJ, Scheithauer BW, Kelly PJ, Jenkins RB (1992) Cytogenetic and loss of heterozygosity studies in ependymomas, pilocytic astrocytomas and oligodendrogliomas. *Genes Chrom Cancer* 5:348–356
2730. Rao C, Friedlander ME, Klein E, Anzil A, Sher JH (1990) Medulloblastoma in an adult. *Cancer* 65:157–163
2731. Rao JS, Steck PA, Tofilon P, Boyd D, Ali-Osman F, Stetler-Stevenson WG, Liotta LA, Sawaja R (1994) Role of plasminogen activator and of 92-KDa type IV collagenase in glioblastoma invasion using an in vitro matrigel model. *J Neurooncol* 18:129–138
2732. Rapoport S (1976) Blood-brain barrier in physiology and medicine. New York, Raven
2733. Rapoport S, Fredericks W, Ohno K, Pettigrew K (1980) Quantitative aspects of reversible opening of the blood-brain barrier. *Am J Physiol* 238:421–431
2734. Rasheed BKA, Bigner SH (1991) Genetic alterations in glioma and medulloblastoma. *Cancer Met Rev* 10:289–299
2735. Rasheed BKA, Fuller GN, Friedman AH, Bigner DD, Bigner SH (1992) Loss of heterozygosity for 10q loci in human gliomas. *Genes Chrom Cancer* 5:75–82
2736. Rasheed BKA, MacLendon RE, Herndon JE, Friedman HS, Friedman AH, Bigner D, Bigner SH (1994) Alterations of the TP53 gene in human gliomas. *Cancer Res* 54:1324–1330
2737. Rasmussen LE, Klatzo I (1969) Proteic and enzyme changes in cold injury edema. *Acta Neuropathol (Berl)* 13:12–28
2738. Rasmussen TB, Kernohan JW, Adson AW (1940) Pathologic classification with surgical considerations of intraspinal tumors. *Ann Surg* 11:513–530
2739. Rath FW, Schneider H, Von Calker H (1974) Histochemische Untersuchungen an Frühstadien experimenteller Hirntumoren. In: Schreiber D, Jänisch W (eds) *Experimentelle Neuroonkologie*. Barth, Leipzig, p 94
2740. Ravens JR, Adamkiewicz LC, Groff K (1955) Cytology and cellular pathology of the oligodendrogliomas of the brain. *J Neuropathol Exp Neurol* 14:142–148
2741. Ravindran M, Radhakrishnan VV, Rao VRK (1980) Communicating cystic craniopharyngioma. *Surg Neurol* 14:230–232
2742. Rawlings CE, Giangaspero F, Burger P, Bullard DE (1988) Ependymomas: a clinico-pathologic study. *Surg Neurol* 29:271–281
2743. Rawlinson DG, Herman MM, Rubinstein LJ (1973) The fine structure of a myxopapillary ependymoma of the filum terminale. *Acta Neuropathol (Berl)* 25:1–13
2744. Raymond AA, Halpin SFS, Alsanjari N, Cook MJ, Kitchen ND, Fish DR, Stevens JM, Harding BN, Scaravilli F, Kendall B, Shorvon SD, Neville BGR (1994) Dysembryoplastic neuroepithelial tumors features in 16 patients. *Brain* 117:461–475.
2745. Reagan TJ, Freiman IS (1973) Multiple cerebral gliomas in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 36:523–528
2746. Reddy EK, Kimler BF, Henderson SD, Morantz RA (1980) Combination of misonidazole and radiation therapy in a rat brain tumor (9L) system. In: Brady LW (ed) *Radiation Sensitizers. Their use in the clinical management of cancer*. Masson, New York, pp 457–471
2747. Reddy EK, Mansfield CM, Hartman GV (1983) Chemodectoma of glomus jugulare. *Cancer* 52:337–340
2748. Reed RJ, Harkin JC (1983) Tumors of the peripheral nervous system, series 2, fascicle 3. AFIP, Washington, pp 25–27
2749. Reese AB (1951) Tumors of the eye. Cassal, London
2750. Reese TS, Karnovsky MJ (1967) Fine structural localization of a bloodbrain barrier to exogenous peroxidase. *J Cell Biol* 34:207–217
2751. Reid LM, Holland J, Jones C, Wolf B, Niwayama G, Williams R, Kaplan NO, Sato G (1978) Some in the variables affecting the success of trasplantation of human tumors into the athymic nude mouse. In: Houchens DP, Ovejera AA (eds) *The use of athymic (nude) mice in cancer research*. Fischer, New York, pp 107–121
2752. Reifenberger G, Szymas J, Wechsler W (1987) Differential expression of glial- and neuronal-associated antigens in human tumors of the central and peripheral nervous system. *Acta Neuropathol (Berl)* 74:105–123
2753. Reifenberger G, Bilzer T, Seitz RJ, Wechsler W (1989) Expression of vimentin and glial fibrillary acidic protein in ethylnitrosourea-induced rat gliomas and glioma cell lines. *Acta Neuropathol (Berl)* 78:270–282



2754. Reifenberger G, Prior R, Deckert M, Wechsler W (1989) Epidermal growth factor receptor expression and growth fraction in human tumors of the nervous system. *Virchows Arch [A] Path Anat His* 414:147–155
2755. Reifenberger G, Liu L, Ichimura K, Schmidt E, Collins VP (1993) Amplification and overexpression of the MDM2 gene in a subset of human malignant gliomas without p53 mutations. *Cancer Res* 53:2736–2739
2756. Reifenberger J, Reifenberger G, Liu L, James CD, Wechsler W, Collins VP (1994) Molecular genetic analysis of oligodendroglial tumors shows preferential allelic deletions on 19q and 1p. *Am J Pathol* 145:1175–1190
2757. Reimer R, Onofrio BM (1985) Astrocytoma of the spinal cord in children and adolescents. *J Neurosurg* 63:669–675
2758. Reinhold HS (1974) Cell viability of the vessel wall. *Curr Top Radiat Res Quart* 10:9–16
2759. Reinhold HS, Hopewell JW (1980) Late changes in the architecture of blood vessels of the rat brain after irradiation. *Br J Radiol* 53:693–696
2760. Reiter RJ (1980) The pineal gland and its hormones in the control of reproduction in mammals. *Endocrine Rev* 1:109–131
2761. Reiter RJ (1981) The mammalian pineal gland: structure and function. *Am J Anat* 162:287–313
2762. Reiter RJ (1983) The pineal gland: an intermediary between the environment and the endocrine system. *Psychoneuroendocrinology* 8:31–40
2763. Remak V (1854) Beitrag zur Entwicklungsgeschichte der krebshaften Geschwülste. *Dtschh Klin* 6:170–174
2764. Rempel SA, Rosenblum ML, Mikkelsen T, Yan PS, Ellis KD, Golembieski WA, Sameni M, Rozhin J, Ziegler G, Sloane BF (1994) Cathepsin B expression and localization in glioma progression and invasion. *Cancer Res* 54:6027–6031
2765. Rengachary SS, Lee SH (1991) Paraganglioma of the cauda equina. In: Wilkins SS, Rengachary SS (eds) *Neurosurgery update II*. McGraw-Hill, New York, pp 29–35
2766. Rengachary SS, Watanabe I (1981) Ultrastructure and pathogenesis of intracranial arachnoid cysts. *J Neuropathol Exp Neurol* 40:61–83
2767. Resnicoff M, Sell C, Rubini M, Copola D, Ambrose D, Baserga R, Rubin R (1994) Rat glioblastoma cells expressing an antisense RNA to the insulin-like growth factor-1 (IGF-1) receptor are nontumorigenic and induce regression of wild-type tumors. *Cancer Res* 54:2218–2222
2768. Rethelgy M (1984) Diffusional barrier around the hypothalamic arcuate nucleus in the rat. *Brain Res* 307:355–358
2769. Reulen HJ, Graham R, Spatz M, Klatzo I (1977) Role of pressure gradients and bulk flow in dynamics of vasogenic brain edema. *J Neurosurg* 46:24–35
2770. Rey JA, Bello MJ, de Campos JM, Kusak ME, Ramos C, Moreno S (1987) Chromosomal composition of a series of 22 human low-grade gliomas. *Cancer Genet Cytogenet* 29:223–227
2771. Rey YA, Pestana A, Bello MJ (1992) Cytogenetics and molecular genetics of nervous system tumors. *Oncol Res* 4:321–331
2772. Reynolds ES (1923) Trauma as a possible cause of brain tumor. *Lancet* 2:13–14
2773. Reznik KM, Schoenen J (1983) Lhermitte-Duclos disease. *Acta Neuropathol (Berl)* 59:88–94
2774. Rhodes RH, Davis RL, Kassel SH, Clague BH (1978) Primary cerebral neuroblastoma: a light and electron microscopic study. *Acta Neuropathol (Berl)* 41:119–124
2775. Ribbert H (1910) Über das Endotheliom der Dura. *Virchows Arch [A] Path Anat His* 200:141–151
2776. Ribbert H (1918) Über das Spongioblastom und das Gliom. *Virchows Arch [A] Path Anat His* 225:195–213
2777. Ribbert H, Steiner H (1894) Über die Echinodermoiden physalifora sphenooccipitalis, nach Untersuchungen von Hermann Steiner. *Zentral Allg Pathol* 5:457–461
2778. Riboli E, Macaluso M (1980) Epidemiologia dei tumori del sistema nervoso. Mortalità italiana, incidenza in provincia di Varese, confronti internazionali. *Atti Secondo Convegno Nazionale di Neuroepidemiologia*, Milano
2779. Riccardi VM (1992) *Neurofibromatosis: phenotype, natural history and pathogenesis*, 2nd edn. Johns Hopkins University Press, Baltimore

2780. Riccardi VM, Eichner JE (1986) Neurofibromatosis. Johns Hopkins University, Baltimore
2781. Rich JN, Elion JB, Wellner B, Colvin OM, Groothuis DR, Hilton JH, Schlageter KE, Bigner DD, Griffith OW, Friedman HS (1995) The effect of L-amino acid oxidase on activity of melphalan against an intracranial xenograft. *Cancer Chemother Pharmacol* 36:379–384
2782. Richard P, McKissock W (1980) Intracranial metastases. In: We L, Gilbert H, Posner J (eds). *Metastases*, Boston, GK Hale, pp 380–389
2783. Richardson EP Jr (1991) Pathology of tuberous sclerosis. *Ann NY Acad Sci* 615:128–139
2784. Richardson WD, Pringle N, Mosley MJ, Westermark B, Dubois-Dalcq M (1988) A role for platelet-derived growth factor in normal gliogenesis in the central nervous system. *Cell* 53:309–319
2785. Richman AV, Balis GA, Maniscalco JE (1980) Primary intracranial tumour with mixed chondrosarcoma and glioblastoma – gliosarcoma or sarcoglioma? *J Neuropathol Exp Neurol* 39:329–335
2786. Richter RB (1951) True hamartoma of the hypothalamus associated with pubertas praecox. *J Neuropathol Exp Neurol* 10:368–383
2787. Rickmann M, Wolf JR (1985) Prenatal gliogenesis in the neopallium of the rat. *Adv Anat Embryol Cell Biol* 93:1–40
2788. Ridley A, Cavanagh JB (1971) Lymphocytic infiltration in gliomas: evidence of possible host resistance. *Brain* 94:117–124
2789. Rieth KG, Kichiro G, London WT, Sever JL, Houff SA, Kornblith PL, McKeever PE, Buonomo C, Padgett BL, Walker DL (1980) Experimental gliomas in primates: a computed tomography model. *J Comput Assist Tomogr* 4:285–290
2790. Rieth KG, Comite F, Dwyer AJ, Nelson NJ, Pescovitz O, Shawker TH, Cutler GB, Loriaux DX (1987) CT of cerebral abnormalities in precocious puberty. *AJR* 148:1231–1238
2791. Riggs HE, Clary WV (1957) A case of intramedullary sheath cell tumor of the spinal cord: consideration of vascular nerve as a source of origin. *J Neuropathol Exp Neurol* 16:332–336
2792. Ringel SP, Bailey OT (1972) Rathke's cleft cysts. *J Neurol Neurosurg Psychiatry* 35:693–697
2793. Ringertz N (1950) Grading of gliomas. *Acta Pathol Microbiol Scand* 27:51–64
2794. Ringertz N (1964) Hamperl H: The nomenclature of tumours of the nervous system. Discussion In: Zülch KJ, Woolf AL (eds) *Classification of brain tumours*. Springer, Vienna, p 9
2795. Ringertz N, Nordenstam H (1951) Cerebellar astrocytoma. *J Neuropathol Exp Neurol* 10:343–367
2796. Ringertz N, Raymond A (1949) Ependymomas and choroid plexus papillomas. *J Neuropathol Exp Neurol* 8:355–380
2797. Ringertz N, Tola JH (1950) Medulloblastoma. *J Neuropathol Exp Neurol* 9:354–372
2798. Ringertz N, Nordenstam H, Flyger G (1954) Tumors of the pineal region. *J Neuropathol Exp Neurol* 13:540–561
2799. Ringsted J (1958) Meningeal tumors with extracranial metastasis, with a case report. *Acta Pathol Microbiol Scand* 43:9–20
2800. Ritland SR, Ganju V, Jenkins RB (1995) Region-specific loss of Heterozygosity on chromosome 19 is related to the morphologic type of human glioma. *Genes Chrom Cancer* 12:277–282
2801. Ritz J, Schlossman SF (1982) Utilization of monoclonal antibodies in the treatment of leukemia and lymphoma. *Blood* 59:1–11
2802. Riva D, Pantaleoni C, Milani N, Fossati Bellani F (1989) Impairment of neuropsychological functions in children with medulloblastomas and astrocytomas in the posterior fossa. *Childs Nerv Syst* 5:107–110
2803. Riva P, Arista A, Tison V, Sturiale C, Franceschi G, Spinelli A, Riva N, Casi M, Moscatelli G, Frattorelli M (1994) Intralesional radioimmunotherapy of malignant gliomas. An effective treatment in recurrent tumors. *Cancer* 73:1076–1082
2804. Riva P, Arista A, Franceschi G, Frattarelli M, Sturiale C, Riva N, Casi M, Rossitti R (1995) Local treatment of malignant gliomas by direct infusion of specific monoclonal antibodies labeled with I-131: comparison of the results obtained in recurrent and newly diagnosed tumors. *Cancer Res* 55:5952–5956
2805. Rizzoli VH, Randall JD, Smith DR (1978) Psammoma bodies in meningioma. Appearance by scanning electron microscopy. *Virchows Arch [A] Pathol Anat Histol* 380:317–325
2806. Robbins KC, Aaronson SA (1988) The sis oncogene. In: Reddy EP, Skalka AM, Curran T (eds) *The oncogene handbook*. Elsevier, Amsterdam, pp 427–452

2807. Roberts M, German WJ (1969) Oligodendroglioma: a 40-year survival. *J Neurosurg* 31:355-357
2808. Robertson DM (1964) Electron microscopic studies of nuclear inclusions in meningiomas. *Am J Pathol* 45:835-848
2809. Robertson DM, Hendry WS, Vogel FS (1964) Central ganglioneuroma: a case study using electron microscopy. *J Neuropathol Exp Neurol* 23:692-705
2810. Robinson RG (1955) Two cerebellar tumours with unusual features. 1. Cystic astrocytoma. 2. Papilloma of the choroid plexus. *J Neurosurg* 12:183-186
2811. Rodesch G, Lasjaunas P (1991) Embolization and meningiomas. In: Al-Mefty O (ed) *Meningiomas*. Raven, New York, pp 285-298
2812. Roelcke U, Radu EW, Vonammon K, Hausmann O, Maguire RP, Leenders KL (1995) Alteration of blood-brain barrier in human brain tumors: Comparison of (F-18)fluorodeoxyglucose, (C-11)methionine and rubidium-82 using PET. *J Neurol Sci* 132:20-27
2813. Roelink H, Nusse R (1991) Expression of two members of the Wnt family during mouse development-restricted temporal and spatial patterns in the developing neural tube. *Genes Dev* 5:381-388
2814. Roessmann U, Velasco ME, Sindely SD, Gambetti P (1980) Glial fibrillary acidic protein (GFAP) in ependymal cells during development. An immunohistochemical study. *Brain Res* 200:13-21
2815. Roessmann U, Velasco ME, Gambetti P, Aulilio-Gambetti (1983) Neuronal and astrocytic differentiation in human neuroepithelial neoplasms. An immunohistochemical study. *J Neuropathol Exp Neurol* 42:113-121
2816. Rogers HM, Long DM, Chou SN, French LA (1971) Lipomas of the spinal cord and cauda equina. *J Neurosurg* 34:349-354
2817. Roggendorf W, Schuster T, Peiffer J (1987) Proliferative potential of meningiomas determined with the monoclonal antibody Ki-67. *Acta Neuropathol (Berl)* 73:361-364
2818. Roholl PJM, Kleyne J, Prine MEF (1989) Immunologic marker analysis of normal and malignant histiocytes. A comparative study of monoclonal antibodies for diagnostic purposes. *Am J Clin Pathol* 89:187-194
2819. Rohringer M, Sutherland GR, Louw D, Sima AAF (1989) Incidence and clinicopathological features of meningiomas. *J Neurosurg* 71:665-672
2820. Roman DD, Sperduto PW (1995) Neuropsychological effects of cranial radiation: current knowledge and future directions. *Int J Radiat Oncol Biol Phys* 13:983-998
2821. Român G, Fischer M, Perl DP, Poser CM (1978) Neurological manifestations of hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber disease): report of 2 cases and review of the literature. *Ann Neurol* 4:130-144
2822. Roman-Goldstein SM, Golgman DL, Howieson J, Neuwelt EA (1992) MR of primary CNS lymphoma in immunologically normal patients. *AJNR* 13:1207-1213
2823. Romanic AM, Madri JA (1994) Extracellular matrix-degrading proteinases in the nervous system. *Brain Pathol* 4:145-156
2824. Romanul FCA (1964) Intramedullary neuromas of the spinal cord. Discussion. *J Neuropathol Exp Neurol* 23:201
2825. Ron E, Modan B, Boice JD, Alfandary E, Stovall M, Chetrit A, Katz L (1988) Tumors of the brain and nervous system after radiotherapy in childhood. *N Engl J Med* 319:1033-1039
2826. Roosen N, Cras P, Paquier P, Martin JJ (1989) Primary thalamic malignant fibrous histiocytoma of the dominant hemisphere causing severe neuropsychological symptoms. *Clin Neuropathol* 8:16-21
2827. Rorke LB (1983) Presidential address. The cerebellar medulloblastoma and its relationship to primitive neuroectodermal tumours. *J Neuropathol Exp Neurol* 42:1-15
2828. Rorke LB (1987) Relationship of morphology of ependymoma in children to prognosis. *Progr Exp Tumor Res* 30:170-174
2829. Rorke LB (1989) Primitive neuroectodermal tumor. A concept requiring an apologia. In: Fields WS (ed) *Primary brain tumors. A review of histologic classifications*. Springer, Berlin Heidelberg New York, pp 5-15
2830. Rorke LB, Gilles FH, Davis RL, Becker LE (1985) Revision of the World Health Organization classification of the brain tumors for childhood brain tumors. *Cancer* 56:1869-1886

2831. Rorke LB, Packer R, Biegel J (1995) Central nervous system atypical teratoid/rhabdoid tumors of infancy and childhood. *J Neurooncol* 24:21–28
2832. Roscoe FP, Claisse PJ (1976) A sequential in vivo–in vitro study of carcinogenesis induced in the rat brain by ethylnitrosourea. *Nature* 262:314–316
2833. Rosen ST, Aisner J, Makuch R (1982) Carcinomatous leptomeningitis in small cell lung cancer. A clinicopathologic review of the National Cancer Institute experience. *Medicine* 61:45–53
2834. Rosenberg GA, Kornfeld M, Estrada E, Kelley RO, Liotta LA, Stetler Stevenson WG (1992) TIMP-2 reduces proteolytic opening of blood brain barrier by type IV collagenase. *Brain Res* 576:203–207
2835. Rosenblum ML, De Tribolet N (1990) Summary of the Eight International Conference on Brain Tumor Research and Therapy. *Neurosurgery* 26:6
2836. Rosenblum ML, Gerosa MA (1984) Stem cell sensitivity. *Prog Exp Tumor Res* 28:1–17
2837. Rosenbluth PR, Lichtenstein BW (1960) Pearly tumor (epidermoid cholesteatoma) of the brain. Clinicopathologic study of two cases. *J Neurosurg* 17:35–42
2838. Rosenblum ML, Gerosa MA, Wilson CB (1983) Stem cell studies of human malignant brain tumors. Part 1: development of stem cell assay and its potential. *J Neurosurg* 58:170–176
2839. Rosenblum ML, Gerosa MA, Bodell WJ, Talcott RL (1984) Tumor cell resistance. *Progr Exp Tumor Res* 27:191–214
2840. Rosenblum ML, Delattre JY, Walker RW, Shapiro WR (1989) Fatal necrotizing encephalopathy complicating treatment of malignant gliomas with intra-arterial BCNU and irradiation: a pathological study. *J Neurooncol* 7:269–281
2841. Rosenblum ML, Eisenberg AO, Norman D (1992) Brain tumor invasion: clinical patterns of malignant astrocytoma spread. *J Neurosurg* 76:383A
2842. Rosenfeld J, Rossi ML, Briggs M (1989) Glioblastoma multiforme of the cerebellum in an elderly man. *Tumori* 75:626–629
2843. Rosenfeld MG (1991) POU-domain transcription factors: POU-er-ful developmental regulators. *Genes Dev* 5:897–907
2844. Rosengren LE, Aurell A, Kjellstrand P (1985) Astrogliosis in the cerebral cortex of gerbils after long-term exposure to 1,1,1-trichloroethane. *Scand J Work Environ Health* 11:447–455
2845. Rossnawasser H (1958) Metastases from glomus jugulare tumors. *Arch Otolaryng* 41:64–70
2846. Ross DA, Edwards MSB, Wilson CB (1986) Intramedullary neurinomas of the spinal cord: report of two cases and review of the literature. *Neurosurgery* 19:458–464
2847. Ross GW, Rubinstein LJ (1989) Lack of histopathological correlation of malignant ependymomas with postoperative survival. *J Neurosurg* 70:31–36
2848. Ross JB, Robitaille Y, Villemure JG, Tampieri D (1991) Diagnosis and management of gliomatosis cerebri: recent trends. *Surg Neurol* 36:431–440
2849. Ross-Riveros P, Leith JT (1979) Response of 9L tumor cells to hyperthermia and X irradiation. *Radiat Res* 78:296–301
2850. Rossi ML, Hughes JT, Esiri MM, Coakham HB, Brownell DB (1987) Immunohistological study of mononuclear cell infiltrate in malignant gliomas. *Acta Neuropathol (Berl)* 74:269–277
2851. Rossi ML, Cruz-Sanchez F, Hughes JT, Esiri MM, Coakham HB, Moss TH (1988) Mononuclear cell infiltrate and HLA-DR expression in low grade astrocytomas. *Acta Neuropathol (Berl)* 76:821–826
2852. Rossi ML, Jones NR, Candy E, Nicoll JAR, Compton JS, Hughes JT, Esiri MM, Moss TH, Cruz-Sanchez F, Coakham HB (1989) The mononuclear cell infiltrate compared with survival in high-grade astrocytomas. *Acta Neuropathol (Berl)* 78:189–193
2853. Roszman TL, Brooks WM, Elliott LH (1982) Immunology of primary intracranial tumors. IV. Suppressor cell functional lectin binding lymphocyte subpopulations in patients with cerebral tumors. *Cancer* 50:1273–1279
2854. Roszman TL, Elliot L, Brooks W (1991) Modulation of T-cells function by gliomas. *Immunol Today* 12:370–374
2855. Rottenberg DA, Chernik NL, Deck MDF, Ellis F, Posner JB (1977) Cerebral necrosis following radiotherapy of extracranial neoplasms. *Ann Neurol* 1:339–357
2856. Rouah E, Wilson DR, Armstrong DL, Darlington GJ (1989) N-myc amplification and neuronal differentiation in human primitive neuroectodermal tumors of the central nervous system. *Cancer Res* 49:1797–1801

2857. Rouleau GA, Seizinger BR, Werteleki W, Haines JL, Superneau DW, Martuza RL, Gusella JF (1990) Flanking markers bracket the neurofibromatosis type 2 (NF2) gene on chromosome 22. *Am J Hum Genet* 46:323–328
2858. Rouleau GA, Merel P, Lutchman M, Sanson M, Zucman J, Marineau C, Hoang XK, Demczuk S, Desmaze C, Plougastel B, Pulst SM, Lenoir G, Biljsma E, Fashold R, Dumanski J, de Jong P, Parry D, Eldridge R, Aurias A, Delattre O, Thomas G (1993) Alteration in a new gene encoding a putative membrane-organizing protein causes neurofibromatosis type 2. *Nature* 363:515–521
2859. Roussy G, Cornil L (1928) A propos de la classification des tumeurs des méninges. *Rev Neurol (Paris)* 49:122–125
2860. Roussy G, Lhermitte J, Cornil L (1924) Essai de classification des tumeurs cérébrales. *Ann Anat Pathol* 1:333–378
2861. Roussy G, Oberling Ch (1931) Atlas du cancer. Félix Alcan, Paris
2862. Roussy G, Oberling C, Raileanu C (1931) Les neurospongiomes. *Press Med* 12:977–981
2863. Rout D, Das L, Rao VRK, Radhakrishnan VV (1983) Symptomatic Rathke's cleft cysts. *Surg Neurol* 19:42–45
2864. Rubinfeld M, Abramson DH, Ellsworth RM, Kitchin FD (1986) Unilateral vs bilateral retinoblastoma. Correlations between age at diagnosis and stage of ocular disease. *Ophthalmology* 93:1016–1021
2865. Rubinstein AB, Shalit MN, Cohen ML, Sandbank U, Reichenthal E (1984) Radiation-induced cerebral meningioma: a recognizable entity. *J Neurol* 61:966–971
2866. Rubinstein LJ (1956) The development of contiguous sarcomatous and gliomatous tissue in intracranial tumors. *J Pathol Bacteriol* 71:441–459
2867. Rubinstein LJ (1963) Tumeurs et hamartomes dans la neurofibromatose centrale. In: Michaux L, Feld M (eds) *Les phacomatoses cérébrales*. SPEI, Paris, pp 427–438
2868. Rubinstein LJ (1964) Morphological problems of brain tumors with mixed cell population. In: Zülch KJ, Woolf AL (eds) *Classifications of brain tumors*. Springer, Vienna, p 141
2869. Rubinstein LJ (1970) The definition of ependymoblastoma. *Arch Pathol* 90:35–45
2870. Rubinstein LJ (1971) Sarcomas of the nervous system. In: Minckler J (ed) *Pathology of the nervous system*, vol 2. McGraw-Hill, New York, pp 2144–2164
2871. Rubinstein LJ (1972) Tumors of the central nervous system. Armed Forces Institute of Pathology, Washington (Atlas of tumor pathology, 2nd series, fascicle 6)
2872. Rubinstein LJ (1974) The cerebellar medulloblastoma: its origin, differentiation, morphological variants and biological behavior. In: Vinken PJ, Bruyn GW (eds) *Handbook of clinical neurology*, vol 18. North-Holland, Amsterdam, pp 167–193
2873. Rubinstein LJ (1985) Embryonal central neuroepithelial tumors and their differentiating potential. A cytogenetic view of a complex neuro-oncological problem. *J Neurosurg* 62:795–805
2874. Rubinstein LJ (1986) Immunohistochemical signposts – not markers – in neuronal tumour differentiation. *Neuropathol Appl Neurobiol* 12:523–537
2875. Rubinstein LJ (1986) The malformative central nervous system lesions in the central and peripheral forms of neurofibromatosis. A neuropathological study of 22 cases. *Ann NY Acad Sci* 486:14–29
2876. Rubinstein LJ (1987) The correlation of neoplastic vulnerability with central neuroepithelial cytogeny and glioma differentiation. *J Neurooncol* 5:11–27
2877. Rubinstein LJ (1989) Comment to: Onda K et al. *J Neurosurgery* 25:540
2878. Rubinstein LJ, Brucher JM (1981) Focal ependymal differentiation in choroid plexus papillomas. An immunoperoxidase study. *Acta Neuropathol (Berl)* 53:29–33
2879. Rubinstein LJ, Herman MM (1972) A light- and electron microscopic study of a temporal-lobe ganglioglioma. *J Neurol Sci* 16:27–48
2880. Rubinstein LJ, Herman MM (1989) The astroblastoma and its possible cytogenetic relationship to the tanycyte. An electron microscopic, immunohistochemical, tissue- and organ-culture study. *Acta Neuropathol (Berl)* 78:472–483
2881. Rubinstein LJ, Logan WJ (1970) Extraneural metastases in ependymoma of the cauda equina. *J Neurol Neurosurg Psychiatry* 33:763–770
2882. Rubinstein LJ, Northfield DWC (1964) The medulloblastoma and the so-called “arachnoidal cerebellar sarcoma”: a critical re-examination of a nosological problem. *Brain* 87:379–412

2883. Rubinstein LJ, Okazaki H (1970) Gangliogliomatous differentiation in a pineocytoma. *J Pathol* 102:27–32
2884. Rubinstein LJ, Sutton CH (1964) Histochemical observations on oxidative enzyme activity in tumors of the nervous system. *J Neuropathol Exp Neurol* 23:196
2885. Rubinstein LJ, Herman MM, Hanberg JW (1974) The relationship between differentiating medulloblastoma and dedifferentiating cerebellar astrocytoma. Light, electron microscopic, tissue, and organ culture observation. *Cancer* 33:675–690
2886. Rubinstein LJ, Herman MM, VanderBerg SR (1984) Differentiation and anaplasia in central neuroepithelial tumors. *Progr Exp Tumor Res* 27:32–48
2887. Rubio MP, von Deimling A, Yandell DW, Wiestler OD, Gusella JF, Louis DN (1993) Accumulation of wild type p53 protein in human astrocytomas. *Cancer Res* 53:3465–3467
2888. Rubio MP, Correa KM, Ramesh V, MacCollin MM, Jacoby LB, von Deimling A, Gusella JF, Louis DN (1994) Analysis of the neurofibromatosis 2 (NF2) gene in human ependymomas and astrocytomas. *Cancer Res* 54:45–47
2889. Rucklidge GJ, Dean V, Robins SP, Mella O, Bjerkvig R (1989) Immunolocalization of extracellular matrix proteins during brain tumor invasion in BD-IX rats. *Cancer Res* 49:5419–5423
2890. Rucklidge GJ, Lund-Johansen M, Milne G, Bjerkvig R (1990) Isolation and characterization of a metalloproteinase secreted by rat glioma cells in serum-free culture. *Biochem Biophys Res Comm* 172:544–550
2891. Ruiz i Altaba A (1994) Pattern formation in the vertebrate neural plate. *TINS* 6:233–243
2892. Ruoslahti E, Engvall E, Hayman EG (1981) Fibronectin: current concepts of its structure and function. *Collagen Rel Res* 1:95–128
2893. Rüschoff J, Plate K, Bittinger A (1989) Application of the AgNOR method to cell imprints. *J Pathol* 158:333
2894. Rush JA, Young BR, Campbell RJ et al (1982) Optic glioma: long-term follow-up of 85 histopathologically verified cases. *Ophthalmology* 89:1213–1219
2895. Rush JL, Kusske JA, De Feo DR, Pribram HW (1975) Intraventricular craniopharyngioma. *Neurology* 25:1094–1096
2896. Russell DS (1949) Observations on the pathology of hydrocephalus. Special report series no. 265, Medical Research Council. HM Stationery Office, London
2897. Russell DS (1955) Polar spongioblastomas: their place in the glioma series. II. Intern. Congr. Neuropath., London, *Exc Med Neur Psych* 8:818
2898. Russell DS, Cairns H (1947) Polar spongioblastomas. *Arch Histol Norm Pathol* 3:423–441
2899. Russell DS, Rubinstein LJ (1959) Pathology of tumours of the nervous system, 1st edn. Arnold, London
2900. Russell DS, Rubinstein LJ (1962) Ganglioglioma: a case with long history and malignant evolution. *J Neuropathol Exp Neurol* 21:185–193
2901. Russell DS, Rubinstein LJ (1963) Pathology of tumours of the nervous system, 2nd edn. Arnold, London
2902. Russell DS, Rubinstein LJ (1971) Pathology of tumours of the nervous system, 3rd edn. Arnold, London
2903. Russell DS, Rubinstein LJ (1977) Pathology of tumours of the nervous system, 4th edn. Arnold, London
2904. Russell DS, Rubinstein LJ (1989) Pathology of tumours of the nervous system, 5th edn. Arnold, London
2905. Russell DS, Wilson CW, Tansley K (1949) Experimental radionecrosis in the brain of rabbits. *J Neurol Neurosurg Psychiatry* 12:187–195
2906. Russell SJ, Ye Y-W, Waber PG, Shuford M, Schold SC, Nisen PD (1995) p53 mutations, O6-alkylguanine DNA alkyltransferase activity, and sensitivity to procarbazine in human brain tumors. *Cancer* 75:1339–1342.
2907. Rusyniak WG, Marchese MJ, Nelson CN (1992) Benign meningioma with a short latency period following irradiation. *Surg Neurol* 38:261–264
2908. Rutherford GS, Marus G (1987) Microcystic meningiomas. *Clin Neuropathol* 6:143–148
2909. Rutigliano MJ, Lunsford LD, Kondziolka D, Strauss MJ, Khanna V, Green M (1995) The cost effectiveness of stereotactic radiosurgery versus surgical resection in the treatment of solitary metastatic brain tumors. *Neurosurgery* 37:445–453

2910. Rutka JT, Apodaca G, Stern R, Rosenblum M (1988) The extracellular matrix of the central and peripheral nervous systems: structure and function. *J Neurosurg* 69:155-170
2911. Rutledge MH, Sarrazin J, Rangaratnam S, Phelan CM, Twist E, Merel P, Delattre O, Thomas G, Nordenskjold M, Collins VP, Dumanski JP, Rouleau GA (1994) Evidence for the complete inactivation of the NF 2 gene in the majority of the sporadic meningiomas. *Nature Genet* 6:180-184
2912. Rutzel H, Schiebler TH (1980) Prenatal and early post-natal development of the glial cells in the median eminence of the rat. *Cell Tiss Res* 211:117-137
2913. Safdari H, Boluix B, Gros C (1984) Multifocal brain radionecrosis masquerading as tumor dissemination. *Surg Neurol* 21:35-41
2914. Safdari H, Hochberg FH, Richardson EP Jr (1985) Prognostic value of round-cell (lymphocyte) infiltration in malignant gliomas. *Surg Neurol* 23:221-226
2915. Safdari H, Fuentes JM, Dubois JB, Alizerai M, Castan P, Vlahoritch B (1985) Radiation necrosis of the brain: time of onset and incidence related to total dose and fractionation of radiation. *Neuroradiology* 27:44-47
2916. Sagerman RH, Bagshaw MA, Hanbery J (1965) Considerations in the treatment of ependymoma. *Radiology* 84:401-408
2917. Sagerman RH, Collier LM, King GA (1983) Radiation therapy of microgliomas. *Radiology* 149:567-570
2918. Sainz J, Huynh DP, Figueroa K, Ragge NK, Baser ME, Pulst S-M (1994) Mutations of neurofibromatosis type 2 gene and lack of the gene product in vestibular schwannoma. *Hum Molec Genet* 3:885-891
2919. Sakaguchi M, Kajio T, Kawahara K, Kato K (1988) Antibodies against basic fibroblast growth factor inhibit autocrine growth of pulmonary artery endothelial cells. *FEBS Lett* 233:163-166
2920. Sakai H, Kawano N, Okado K et al (1981) A case of pleomorphic xanthoastrocytoma (Kepes). *Neurol Surg (Japan)* 9:1519-1524
2921. Sakaki S, Mori Y, Motozaki T, Nakagawa K, Matsuoka K (1981) A cerebral neuroblastoma with extracranial metastases. *Surg Neurol* 16:53-59
2922. Sakamoto K, Kobayashi N, Ohtsubo H, Tanaka Y (1986) Intracranial tumors in the first year of life. *Childs Nerv Syst* 2:126-129
2923. Salamon M (1995) Experimental therapy for brain tumors. In: Kaye AH, Laws ER Jr (eds) *Brain tumors*. Churchill Livingstone, New York, pp 369-385
2924. Salazar OM (1983) A better understanding of CNS seeding and a brighter outlook for post-operatively irradiated patients with ependymomas. *Int J Radiat Oncol Biol Phys* 9:1231-1234
2925. Salazar OM, Castro-Vita H, VanHoute P, Rubin P, Aygun C (1983) Improved survival in cases of intracranial ependymoma after radiation therapy. *J Neurosurg* 59:652-659
2926. Salzman M (1991) Hyperthermia. In: Salzman M (ed) *Neurobiology of brain tumors*. Williams and Wilkins, Baltimore, pp 359-373
2927. Salzman M (1991) Malignant meningiomas. In: Al-Mefty O (ed) *Meningiomas*. Raven, New York, pp 75-85
2928. Salzman M (1995) Experimental therapy for brain tumors. In: Kaye AH, Laws ER (eds) *Brain tumors*. Churchill Livingstone, New York, pp 369-385
2929. Salzman M, Broadwell RD (1991) The blood-brain barrier. In: Salzman M (ed) *Neurobiology of brain tumors*. Williams and Wilkins, Baltimore, pp 229-250
2930. Salzman M, Mayer R (1984) Intramedullary subependymoma of the cervical spinal cord: case report. *Neurosurgery* 14:608-611
2931. Salzman M, Solomon L (1984) Occurrence of glioblastoma multiforme in three generations of a cancer family. *Neurosurgery* 14:557-561
2932. Saleh J, Silberstein HJ, Salner AL, Uphoff DF (1991) Meningioma: the role of a foreign body and irradiation in tumor formation. *Neurosurgery* 29:113-119
2933. Salibi SS, Nauta HJW, Breem H, Epstein JI, Cho KR (1989) Lipomeningioma: report of three cases and review of the literature. *Neurosurgery* 25:122-126
2934. Sallinen PK, Haapasalo HK, Visakorpi T, Helen PT, Rantala IS, Isola JJ, Helin HJ (1994) Prognostication of astrocytoma patient survival by Ki-67 (MIB-1), PCNA, and S-phase fraction using archival paraffin-embedded samples. *J Pathol* 174:275-282

2935. Salmon I, Kiss R, Levivier M, Rummelink M, Pasteels JL, Brothi J, Flament-Durand J (1993) Characterization of nuclear DNA content, proliferation index, and nuclear size in a series of 181 meningiomas, including benign primary, recurrent, and malignant tumors. *Am J Surg Pathol* 17:239–247
2936. Salvati M, Artico M, Caruso R, Rocchi G, Ramundo Orlando E, Nucci F (1991) A report on radiation-induced gliomas. *Cancer* 67:392–397
2937. Samii M, Bini W (1991) Surgical treatment of craniopharyngiomas. *Zbl Neurochir* 52:17–23
2938. Samii M, Tatagiba M (1995) Craniopharyngioma. In: Brain tumors, Kaye AH, Laws Jr ER (eds), Churchill Livingstone, Edinburgh
2939. Samuels V, Barrett JM, Bockman S, Pantazis CG, Allen MB Jr (1989) Immunocytochemical study of transforming growth factor expression in benign and malignant gliomas. *Am J Pathol* 134:835–902
2940. San-Galli F, Vignaud P, Robert J, Coindre JM, Cohandon F (1989) Assessment of the experimental model of transplanted C6 glioblastoma in Wistar rats. *J Neurooncol* 7:299–304
2941. Sandberg AA (1990) The chromosomes in human cancer and leukemia, 2nd edn. Elsevier, New York, pp 900–908
2942. Sanders BM, White GC, Draper GJ (1981) Occupation of fathers of children dying from neoplasms. *J Epidemiol Community Health* 35:245–250
2943. Sanes JR (1983) Roles of extracellular matrix in neural development. *Annu Rev Physiol* 45:581–600
2944. Sanford RA, Muhlbauer MS (1991) Craniopharyngioma in children. In: Cohen ME, Duffner PK (eds) Brain tumors in children. *Neurol Clin* 9:453–465
2945. Sano K (1987) Problems in the treatment of children with brain tumors. *Prog Exp Tum Res* 30:1–9
2946. Sano K, Matsutani M (1981) Pinealoma (germinoma) treated by direct irradiation. A long-term follow-up. *Childs Brain* 8:81–97
2947. Sano K, Wakai S, Ochiai C, Takakura K (1981) Characteristics of intracranial meningiomas in childhood. *Childs Brain* 8:98–106
2948. Sanson M, Sturtz F (1995) Gene therapy: a treatment for malignant gliomas? *Rev Neurol (Paris)* 151:529–531
2949. Sant M, Crosignani P, Bordo MB, Nicola G, Bianchi M, Berrino F (1988) Incidence and survival of brain tumours: a population-based study. *Tumori* 74:243–252
2950. Saris SC, Blasberg RG, Carson RE, deVroom HL, Lutz R, Dedrick RL, Pettigrew K, Chang R, Doppman J, Wright DC, Herscovitch P, Oldfield EH (1991) Intravascular streaming during carotid artery infusions. *J Neurosurg* 74:763–772
2951. Sarkar C, Roy S, Tandon PN (1988) Oligodendroglial tumors. An immunohistochemical and electron microscopic study. *Cancer* 61:1862–1866
2952. Sarmiento J, Ferrer K, Pons L, Ferrer E (1979) Cerebral mixed tumour: osteo-chondrosarcoma-glioblastoma multiforme. *Acta Neurochir (Wien)* 50:335–341
2953. Sarnat HB (1992) Regional differentiation of the human fetal ependyma: immunocytochemical markers. *J Neuropathol Exp Neurol* 51:58–75
2954. Sasanelli F, Beghi E, Kurland LT (1983) Primary intraspinal neoplasms in Rochester, Minnesota, 1935–1981. *Neuroepidemiology* 2:146–163
2955. Sato A, Tamura A, Sano K (1975) Brain tumors of early infants. *Childs Brain* 1:121–125
2956. Sato K, Kubota T, Yamamoto S, Ishikura A (1986) An ultrastructural study of mineralization in craniopharyngiomas. *J Neuropathol Exp Neurol* 45:463–470
2957. Sato T, Shimoda A, Takahashi T, Daita G, Goto S, Takamura H, Hirama M (1980) Congenital cerebellar neuroepithelial tumor with multiple divergent differentiations. *Acta Neuropathol (Berl)* 50:143–146
2958. Satran R, Lapham LW, Kido DR (1984) Radionécrose cérébrale tardive après irradiation conventionnelle des tumeurs cérébrales. *Rev Neurol (Paris)* 4:249–255
2959. Savitz DA, Loomis DP (1995) Magnetic field exposure in relation to leukemia and brain cancer mortality among electric utility workers. *Am J Epidemiol* 141:123–134
2960. Sawa H, Takeshita I, Kuramitsu M, Fukui M, Inomata H (1987) Immunohistochemistry of retinoblastomas. *J Neurooncol* 5:351–355
2961. Sawada T (1967) The fine structure of gliomas. *Acta Med Fukuoka* 37:47–51



2962. Saxena A, Clark C, Robertson JT, Ikejiri B, Oldfield EH, Ali IU (1992) Evidence for the involvement of a potential second tumor suppressor gene on chromosome 17 distinct from p53 in malignant astrocytomas. *Cancer Res* 52:6716–6721
2963. Saylors RL, Sidransky D, Friedman HS, Bigner SH, Bigner DD, Vogelstein B, Brodeur GM (1991) Infrequent p53 gene mutations in medulloblastoma. *Cancer Res* 51:4721–4723
2964. Sayre GP (1964) The system of grading of gliomas. In: Zülch KJ, Woolf AL (eds) *Classification of brain tumours*. Springer, Vienna, pp 98–106
2965. Sayre GP (1964) The system of grading of gliomas. In: Zülch KJ, Woolf AL (eds) *Classification of brain tumours*. Springer, Vienna, pp 98–106
2966. Schachenmayr W (1967) Über die Entwicklung von Ependym und Plexus Chorioideus der Ratte. *Z Zellforsch* 77:25–68
2967. Schachenmayr W, Friede RL (1978) The origin of subdural neomembranes. I. Fine structure of the dura–arachnoid interface in man. *Am J Pathol* 92:53–61
2968. Schachner M (1982) Cell type-specific surface antigens in the mammalian nervous system. *J Neurochem* 39:1–8
2969. Schachner M, Hedley-White ET, Hsu DW, Schoonmaker G, Bignami A (1977) Ultrastructural localization of glial fibrillary acidic protein in mouse cerebellum by immunoperoxidase labeling. *J Cell Biol* 75:67–73
2970. Schackert G, Fan D, Nayar R, Fidler I (1989) Arrest and retention of multilamellar liposomes in the brain of normal mice or mice bearing experimental brain metastases. *Select Cancer Ther* 5:73–79
2971. Schaerer JP, Woosley RD (1960) Intraventricular meningiomas of the fourth ventricle. *J Neurosurg* 17:337–341
2972. Schaper A (1897) Die frühesten Differenzierung Vorgänge im Centralnervensystem. *Arch Entwicklunsgmech Organism* 5:81–132
2973. Scheinker IM (1945) Subependymoma: a newly recognized tumor of subependymal derivation. *J Neurosurg* 2:232–240
2974. Scheinker IM (1948) *Neurosurgical pathology*. Thomas, Springfield
2975. Scheithauer BW (1978) Symptomatic subependymoma. Report of 21 cases with review of the literature. *J Neurosurg* 49:689–696
2976. Scheithauer BW (1990) Tumors of the meninges. Proposed modifications of the World Health Organization classification. *Acta Neuropathol (Berl)* 80:343–354
2977. Scheithauer BW, Rubinstein LJ (1978) Meningeal mesenchymal chondrosarcoma: report of eight cases with review of the literature. *Cancer* 42:2744–2752
2978. Scheithauer BW, Rubinstein LJ (1979) Cerebral medulloepithelioma. Report of a case with multiple divergent neuroepithelial differentiation. *Childs Brain* 5:62–71
2979. Scheithauer W, Hirose T, Lopes MBS, Gerber HA, Hukee MJ, Charlesworth JC, Li S, Altermath HJ, VandenBerg SR, Shepard C (1995) Subependymal giant cell astrocytoma and tuber: an immunochemical, ultrastructural and immunoelectromicroscopic study. In: *National Tuberous Sclerosis Association 20th Anniversary International Symposium*, pp 47–49
2980. Schelper R, Anderson M (1994) Apoptosis in glial neoplasm: implication for tumor grading and future therapy. *Brain Pathol* 4:436.
2981. Scherer E (1936) Die extramedullären pialen Lipome an der hinteren Wurzellinie des Rückenmarks (kasuistischer Beitrag). *Z Gesamte Neurol Psychiatr* 154:507–520
2982. Scherer HJ (1933) Gliomstudien: I. Die Bedeutung des Mesenchym in Gliomen. *Virchows Arch* 291:321–340
2983. Scherer HJ (1938) La glioblastomatose en plaques: sur les limites anatomiques de la gliomatose et des processus sclérotiques progressifs (sclérose en plaques, sclérose diffuse de Schilder, sclérose concentrique). *J Belg Neurol Psychiatr* 38:1–17
2984. Scherer HJ (1940) The forms of growth in gliomas and their practical significance. *Brain* 63:1–35
2985. Schiavichi P, Kraus-Ruppert R (1980) Familial brain tumors: rhombencephalon-astrocytoma grade I in father and son. *Acta Neuropathol (Berl)* 52:153–155
2986. Schiering M, Phillips MI, Raizada MK, Hermann K (1986) Localization of renin in brain glial cells and neurons, co-localization with angiotensin II. *Fed Proc* 45:174–178
2987. Schiffer D (1959) Ricerche cariomorfologiche nei tumori gliali. *Min Neurochir* 3:147–156

1988. Schiffer D (1971) Calcification in nervous tissue. In: Minckler J (ed) *Pathology of the nervous system*, vol 2. McGraw-Hill, New York, pp 1342–1360
1989. Schiffer D (1973) On the occurrence of oligodendroglia-like areas in neurinomas experimentally induced in the rat by nitrosourea derivatives. *J Neurol Sci* 19:45–52
1990. Schiffer D (1986) Neuropathology and imaging. The ways in which glioma spreads and varies in its histological aspect. In: Walker MD, Thomas DGT (eds) *Biology of brain tumour*. Nijhoff, Boston, pp 163–172
1991. Schiffer D (1991) Pattern of tumor growth. In: Salzman M (ed) *Neurobiology of brain tumors*. Williams and Wilkins, Baltimore, pp 85–135
1992. Schiffer D (1995) The value of immunohistochemistry for the categorization of brain tumors. *J Neuropathol Exp Neurol (Suppl)* 54:59–60
- 1992a. Schiffer D, Borsotti L, Schiffer P, Terreni A (1995) Histological malignancy and recurrence of meningiomas. *Crit Rev Neurosurg* 5:262–269
1993. Schiffer D, Fabiani A (1972) Contribution of histochemistry to knowledge of brain tumor metabolism. In: Grossi-Paoletti E, Paoletti P (eds) *The experimental biology of brain tumors*. Kirsch WM, Thomas, Springfield pp 209–239
1994. Schiffer D, Fabiani A (1975) I tumori cerebrali. *Il Pensiero Scientifico*, Roma
- 1994a. Schiffer D, Gaiani A (1993) Prognostic factors in peripheral nervous system tumors. *Crit Rev Neurosurg* 3:313–324
1995. Schiffer D, Giordana MT (1974) On the occurrence and significance of acid mucopolysaccharides in oligodendrogliomas experimentally induced in the rat by nitrosourea derivatives. In: Schreiber D, Jänisch W (eds) *Experimentelle Neuroonkologie*. Barth, Leipzig, pp 101–108
1996. Schiffer D, Vesco C (1962) Contribution to histochemical demonstration of some dehydrogenase activities in the human nervous tissue. *Acta Neuropathol (Berl)* 2:103–112
1997. Schiffer D, Vesco C (1963) Histochemical observations about the pattern of tetrazolium reduction, with different substrates, in glial cells of normal and pathological human nervous system. *J Histochem Cytochem* 11:335–341
1998. Schiffer D, Vigliani MC (1993) Prognostic factors in oligodendrogliomas. *Crit Rev Neurosurg* 3:59–65
1999. Schiffer D, Sibour F, Vesco C (1961) Les calcifications dans les tumeurs cérébrales: considérations pathogénétiques. *World Neurol* 2:1069–1082
2000. Schiffer D, Fabiani A, Vesco C (1961) Considerazioni sugli aspetti morfologico-strutturali dell'oligodendroglioma. Studio istologico di 20 casi. *Acta Neurol (Napoli)* 16:683–703
2001. Schiffer D, Fabiani A, Sibour F (1963) Considerazioni su alcuni aspetti del processo di calcificazione nel tessuto nervoso. *Riv Pat Nerv Ment* 84:140–152
2002. Schiffer D, Fabiani A, Vesco C (1964) Histochemical study of Rosenthal fibers. With observations about enzyme activities. *Psych Neurol (Basel)* 147:68–80
2003. Schiffer D, Fabiani A, Monticone GF (1964) Studio istochimico della matrice organica delle calcificazioni nel tessuto nervoso. *Riv Pat Nerv Ment* 85:419–438
2004. Schiffer D, Fabiani A, Monticone GF (1966) Recherches histochimiques sur la structure des calcifications dans le tissu nerveux. *Proc V Intern Congr Neuropath Excerpta Medica* 100:812
2005. Schiffer D, Fabiani A, Monticone GF, Cognazzo A (1966) On the nature of lymphocyte-like cells of medulloblastomata. *Acta Neuropathol (Berl)* 6:290–297
2006. Schiffer D, Fabiani A, Monticone GF (1967) Acid phosphatase and non-specific esterase in normal and reactive glia of human nervous system. A histochemical study. *Acta Neuropathol (Berl)* 9:316–327
2007. Schiffer D, Cognazzo A, Fabiani A, Monticone GF (1968) The mast cells in meningiomas and their relationship with calcifications. *Arch Suiss Neurol Neurochir Psychiatr* 101:72–78
2008. Schiffer D, Croveri G, Pautasso C (1974) Frequenza e significato degli infiltrati linfo-plasmacellulari nei gliomi umani. *Tumori* 60:177–184
2009. Schiffer D, Giordana MT, Pezzotta S, Paoletti P (1976) Chemotherapeutic effects of some alkylating derivatives of nitrosourea on the development of tumors transplacentally induced in rats by ENU. *Acta Neuropathol (Berl)* 34:21–31
2010. Schiffer D, Giordana MT, Pezzotta S, Lechner C, Paoletti P (1978) Cerebral tumors induced by transplacental ENU: study of the different tumoral stages, particularly of early proliferations. *Acta Neuropathol (Berl)* 41:27–31

3011. Schiffer D, Cavicchioli D, Giordana MT, Palmucci L, Piazza A (1979) Analysis of some factors affecting survival in malignant gliomas. *Tumori* 65:119–125
3012. Schiffer D, Giordana MT, Mauro A, Racagni G, Bruno F, Pezzotta S, Paoletti P (1980) Experimental brain tumors by transplacental ENU. Multifactorial study of the latency period. *Acta Neuropathol (Berl)* 49:117–122
3013. Schiffer D, Giordana MT, Soffietti R, Tarenzi L, Bertolotto A (1980) On the nature of the so-called monstrocellular sarcoma of the brain. *Neurosurgery* 6:391–397
3014. Schiffer D, Giordana MT, Paoletti P, Soffietti R, Tarenzi L (1980) Pathology of human malignant gliomas after radiation and chemotherapy. *Acta Neurochir (Wien)* 53:205–216
3015. Schiffer D, Giordana MT, Soffietti R, Tarenzi L (1981) A pathologic study of malignant gliomas operated after radio- and chemotherapy. *Tumori* 67:13–17
3016. Schiffer D, Giordana MT, Soffietti R, Tarenzi L, Milani R, Vasario E, Paoletti P (1981) Radio- and chemotherapy of malignant gliomas. Pathological changes in the normal nervous tissue. *Acta Neurochir (Wien)* 58:37–58
3017. Schiffer D, Giordana MT, Soffietti R, Sciolla R (1982) Histological observations on the regrowth of malignant gliomas after radiotherapy and chemotherapy. *Acta Neuropathol (Berl)* 58:291–299
3018. Schiffer D, Giordana MT, Mauro A, Migheli A (1983) Glial fibrillary acidic protein (GFAP) in human cerebral tumors. An immunohistochemical study. *Tumori* 69:95–104
3019. Schiffer D, Giordana MT, Soffietti R, Sciolla R, Sannazzari GL, Vasario E (1984) Effects of radiotherapy on the astrocytomatous areas of malignant gliomas. *J Neurooncol* 2:167–175
3020. Schiffer D, Giordana MT, Mauro A, Migheli A (1984) GFAP, FVIII/RAG, laminin, and fibronectin in gliosarcomas: an immunohistochemical study. *Acta Neuropathol (Berl)* 63:108–116
3021. Schiffer D, Giordana MT, Mauro A, Migheli A (1986) Immunohistochemistry in neuro-oncology. *Bas Appl Histochem* 30:253–265
3022. Schiffer D, Giordana MT, Mauro A, Germano I, Giaccone G (1986) Immunohistochemical demonstration of vimentin in human cerebral tumors. *Acta Neuropathol (Berl)* 70:209–219
3023. Schiffer D, Giordana MT, Migheli A, Giaccone G, Pezzotta S, Mauro A (1986) Glial fibrillary acidic protein (GFAP) and vimentin in the experimental glial reaction of the rat brain. *Brain Res* 374:110–118
3024. Schiffer D, Giordana MT, Germano I, Mauro A (1986) Anaplasia and heterogeneity of GFAP expression in gliomas. *Tumori* 72:163–170
3025. Schiffer D, Chiò A, Giordana MT, Novero D, Palestro G, Soffietti R, Vasario E (1987) Primary lymphomas of the brain: a clinico-pathologic review of 37 cases. *Tumori* 73:585–592
3026. Schiffer D, Chiò A, Giordana MT, Leone M, Soffietti R (1988) Prognostic value of histologic factors in adult cerebral astrocytoma. *Cancer* 61:1368–1393
3027. Schiffer D, Giordana MT, Mauro A, Migheli A (1988) Reactive astrocytes in the morphologic composition of peripheral areas of gliomas. *Tumori* 74:411–420
3028. Schiffer D, Giordana MT, Vigliani MC (1989) Brain tumor of childhood. Nosological and diagnostic problems. *Child Nerv Syst* 5:220–229
3029. Schiffer D, Giordana MT, Pezzotta P, Soffietti R, Vigliani MC, Villare F (1989) Tumoral transformation of the cell response to brain injury in transplacentally ENU-treated rats. *J Neurooncol* 7:525
3030. Schiffer D, Chiò A, Giordana MT, Mauro A, Migheli A, Vigliani MC (1989) The vascular response to tumor infiltration in malignant gliomas. Morphometric and reconstruction study. *Acta Neuropathol (Berl)* 77:369–378
3031. Schiffer D, Chiò A, Giordana MT, Mauro A, Migheli A, Soffietti R, Vigliani MC (1990) Vascular response to irradiation in malignant gliomas. *J Neurooncol* 8:73–84
3032. Schiffer D, Chiò A, Giordana MT, Migheli A, Palma L, Pollo B, Soffietti R, Tribolo A (1991) Histologic prognostic factors in ependymomas. *Child Nerv Syst* 7:177–182
3033. Schiffer D, Chiò A, Cravioto H, Giordana MT, Migheli A, Soffietti R, Vigliani MC (1991) Ependymoma: internal correlations among pathologic signs and the anaplastic variant. *Neurosurgery* 29:206–210
3034. Schiffer D, Giordana MT, Vigliani MC, Cavalla P (1991) Relationship between glial reaction to a stab wound and tumors development after transplacental ethylnitrosourea in the rat. *Acta Neuropathol (Berl)* 83:30–38

3035. Schiffer D, Chiò A, Giordana MT, Pezzulo T, Vigliani MC (1993) Proliferating cell nuclear antigen expression in brain tumors, and its prognostic role in ependymomas: an immunohistochemical study. *Acta Neuropathol (Berl)* 85:495–502
3036. Schiffer D, Giordana MT, Cavalla P, Vigliani MC, Attanasio A (1993) Immunohistochemistry of glial reaction after injury in the rat: double stainings and markers of cell proliferation. *Int J Devl Neuroscience* 2:269–280
3037. Schiffer D, Cavalla P, Chiò A, Giordana MT, Marino S, Mauro A, Migheli A (1994) Tumor cell proliferation and apoptosis in medulloblastoma. *Acta Neuropathol (Berl)* 87:362–370
3038. Schiffer D, Cavalla P, Di Sapio A, Giordana MT, Mauro A (1995) Mutations and immunohistochemistry of p53 and proliferation markers in astrocytic tumors of childhood. *Child's Nerv Syst* 11:517–522
3039. Schiffer D, Cavalla P, Giordana MT, Chiò A, Dutto A (1995) Heterogeneity and cell loss in the assessment of proliferation potential of brain tumors. *J Neuropathol Exp Neurol* 54:420
- 3039a. Schiffer D, Cavalla P, Migheli A, Chiò A, Giordana MT, Marino S, Attanasio A (1995) Apoptosis and cell proliferation in human neuroepithelial tumors. *Neurosci Lett* 195:81–84
3040. Schiffer D, Cavalla P, Migheli A, Giordana MT, Chiadò-Piat L (1996). Bcl-2 distribution in neuroepithelial tumors: an immunohistochemical study. *J Neurooncol* 27:101–100
3041. Schild SE, Scheithauer BW, Schomberg PJ, Hook CC, Kelly PJ, Frick L, Robinow JS, Buskirk SJ (1993) Pineal parenchymal tumors. Clinical, pathologic, and therapeutic aspects. *Cancer* 72:870–880
3042. Schindler E, Gullotta F (1983) Glial fibrillary acidic protein in medulloblastomas and other embryonic CNS tumors of children. *Virchows Arch [A] Pathol Anat His* 398:263–275
3043. Schisano G, Olivecrona H (1960) Neurinomas of the gasserian and trigeminal root. *J Neurosurg* 17:306–322
3044. Schisano G, Todi D, Nordenstam H (1963) Spongioblastoma polare of the cerebral hemispheres. *J Neurosurg* 20:241–251
3045. Schlegel J, Merdes A, Stumm G, Albert FK, Forsting M, Hynes N, Kiessling M (1994) Amplification of the epidermal-growth-factor-receptor gene correlates with different role behaviour in human glioblastoma. *Int J Cancer* 56:72–77
3046. Schlote W (1966) Behaviour of blastomatous astrocytes in the human cerebral white matter. An electron microscopic study. *J Neuropathol Exp Neurol* 25:173
3047. Schmahl W, Knoedlseder M, Favor J, Davidson D (1993) Defects of neuronal migration and the pathogenesis of cortical malformations are associated with Small eye (Sey) in the mouse, a print mutation at the Pax-6-locus. *Acta Neuropathol (Berl)* 86:126–135
3048. Schmechel D, Marangos PJ, Brightman M (1978) Neuron specific enolase is a molecular marker for peripheral and central neuroendocrine cells. *Nature* 276:834–836
3049. Schmeckel DE, Rakic P (1979) A Golgi study of radial glial cells in developing monkey telencephalon: morphogenesis and transformation into astrocytes. *Anat Embryol* 156:115–152
3050. Schmidbauer M, Budka H, Bruckner R, Vorkapic P (1987) Glioblastoma developing at the site of a cerebellar medulloblastoma treated 6 years earlier. *J Neurosurg* 67:915–918
3051. Schmidbauer M, Budka H, Pilz P (1989) Neuroepithelial and ectomesenchymal differentiation in a primitive pineal tumor (“pineal anlage tumor”). *Clin Neuropathol* 8:7–10
3052. Schmidek HH (1987) The molecular genetics of nervous system tumors. *J Neurosurg* 67:1–16
3053. Schmidek HH, Nielsen SL, Schillel AL, Messer J (1971) Morphological studies of rat brain tumors induced by N-nitrosomethylurea. *J Neurosurg* 34:335–340
3054. Schmidt B, Gherardi R, Poirier J, Caron JP (1984) Craniopharyngiome pédiculé du troisième ventricule. *Rev Neurol (Paris)* 140:281–283
3055. Schmidt EE, Ichimura K, Reifenberger G, Collins VP (1994) CKDN2 (p16/MTS1) gene deletion or CDK4 amplification occurs in the majority of glioblastomas. *Cancer Res* 54:6321–6324
3056. Schmidt MB (1900) Über seltene Spaltbildungen im Bereiche des mittleren Stirnfortsatzes. *Virchows Arch [A] Pathol Anat His* 162:340–370
3057. Schmidt MB (1902) Über die Pacchionischen Granulationen und ihr Verhältniss zu den Sarcomen und Psammomen der Dura mater. *Virchows Arch [A] Pathol Anat* 170:429–464
3058. Schmitt HP (1983) Rapid anaplastic transformation in gliomas in adulthood. *Path Res Pract* 176:313–323

3059. Schmitt HP (1983) Rapid anaplastic transformation of gliomas in childhood. *Neuropediatrics* 14:137–143
3060. Schmitt HP (1983) Trauma und tumor: malignes glioma nach stecksplittverletzung des gehirns. *Fortschr Neurol Psych* 51:227–231
3061. Schmitt HP, Wurster K, Bauer M, Parsch K (1982) Mixed chemodectoma-ganglioneuroma of the conus medullaris region. *Acta Neuropathol (Berl)* 57:275–281
3062. Schmitt SJ, Vogel H (1986) Meningiomas. Diagnostic value of immunoperoxidase staining for epithelial membrane antigen. *Am J Surg Pathol* 10:640–645
3063. Schmittgraff A, Hummel M, Anagnostopoulos I, Stein H (1995) AIDS-related primary brain lymphoma. Immunophenotypical and molecular genetic characterization of stereotactic biopsies and of autopsy and cerebrospinal fluid samples. *Pathologie* 1:75–80
3064. Schnegg JF, Gomez F, LeMarchand-Beraud T, Tribolet N (1981) Presence of sex steroid hormone receptors in meningioma tissue. *Surg Neurol* 15:415–418
3065. Schneider M, Obringer AC, Zackai E, Meadows AT (1986) Childhood neurofibromatosis risk factors for malignant disease. *Cancer Genet Cytogen* 21:347–354
3066. Schnitzer J, Franke WW, Schachner M (1981) Immunocytochemical demonstration of vimentin in astrocytes and ependymal cells of developing and adult mouse nervous system. *J Cell Biol* 90:435–447
3067. Schnitzer J, Sommer I, Lagenar C, Berg GS, Schachner M (1983) Immunological characterization of cell types in the cerebellum. In: Battistin L, Hashim GA, Lastha A (eds) *Clinical and biological aspects of peripheral nerve disease*. Liss, New York, pp 301–319
3068. Schober R, Bayindir C, Canbolat A, Urich H, Wechsler W (1992) Gliofibroma: immunohistochemical analysis. *Acta Neuropathol (Berl)* 83:207–210
3069. Schober R, Reifenberger G, Kremer G, Urich H (1993) Symmetrical neurofibroma with Schwann cells predominance and focal formation of microneurinoma. *Acta Neuropathol (Berl)* 85:227–232
3070. Schochet SS Jr, Peters B, O'Neal J, McCormick WF (1975) Intracranial esthesioneuroblastoma: a light and electron microscopic study. *Acta Neuropathol (Berl)* 31:181–189
3071. Schochet SS Jr, Violet TW, Nelson J, Pelofsky S, Barnes PA (1984) Polar spongioblastoma of the cervical spinal cord: case report. *Clin Neuropathol* 3:225–227
3072. Schöder R, Bien K, Meyers I, Vössing R (1991) The relationship between Ki-67 labeling and mitotic index in gliomas and meningiomas: demonstration of the variability of the intermitotic cycle time. *Acta Neuropathol (Berl)* 82:389–294
3073. Schoenberg BS (1978) Epidemiology of primary nervous system neoplasms. In: Schoenberg BS (ed) *Neurological epidemiology: principles and clinical applications*. Raven, New York, pp 475–493
3074. Schoenberg BS (1983) The epidemiology of central nervous system tumors. In: Walker MD (ed) *Oncology of the nervous system*. Nijhoff, Boston, pp 1–29
3075. Schoenberg BS (1991) Epidemiology of primary intracranial neoplasms: disease distribution and risk factors. In: Salzman M (ed) *Neurobiology of brain tumors*. William and Wilkins, Baltimore, pp 3–18
3076. Schoenberg BS, Christine BW, Whisnant JP (1975) Nervous system neoplasms and primary malignancies of other sites. The unique association between meningiomas and breast cancer. *Neurology* 25: 705–712
3077. Schoenberg BS, Christine BW, Whisnant JP (1976) The descriptive epidemiology of primary intracranial neoplasms – the Connecticut experience. *Am J Epidemiol* 104:449–510
3078. Schoenberg BS, Schoenberg DG, Christine BW (1976) The epidemiology of primary intracranial neoplasms of childhood: a population study. *Mayo Clin Proc* 51:51–56
3079. Schofield D, West DC, Anthony DC, Mashal R, Sklar J (1995) Correlation of loss of heterozygosity at chromosome 9q with histologic subtype in medulloblastomas. *Am J Pathol* 146:472–480
3080. Schold SC, Friedman HS, Brent TP, Bigner SH, Bigner DD (1989) O6-alkylguanine-DNA alkyltransferase in primary central nervous system neoplasms. *J Neurooncol* 7 [Suppl]:90
3081. Schold SC, Bigner DD (1983) A review of animal brain tumor models that have been used for therapeutic studies. In: Walker MD (ed) *Oncology of the nervous system*. Nijhoff, Boston, pp 31–63

3082. Scholtz W (1935) Über die Empfindlichkeit des Gehirns für Röntgen- und Radiumstrahlen. *Klin Wochenschr* 14:189–193
3083. Schopp R (1969) Primäre Geschwulste in der Karotisgabel. Beitrag zur Pathologie, Klinik und Kasuistik. *Munch Med Wochenschr* 111:1558–65
3084. Schor SL, Grey AM, Picardo M, Schor A, Howell A, Ellis I, Rushton G (1991) Heterogeneity amongst fibroblasts in the production of migration stimulating factor (MSF): Implications for cancer pathogenesis. In: Goldberg ID (ed) *Cell motility factors*. Birkhauser, Basel, pp 127–146
3085. Schott B, Robert J (1989) Comparative cytotoxicity, DNA synthesis inhibition and drug incorporation of eight anthracyclines in a model of doxorubicin-sensitive and -resistant rat glioblastoma cells. *Biochem Pharmacol* 38:167–172
3086. Schottenfeld D, Warshauer ME, Sherlock S (1980) The epidemiology of testicular cancer in young adults. *Am J Epidemiol* 112:232–246
3087. Schrantz JL, Araoz CA (1972) Radiation induced meningeal fibrosarcoma. *Arch Pathol* 93:26–31
3088. Schreier HA, Sherry N, Shaughnessy E (1977) Lead poisoning and brain tumors in children: a report of 2 cases. *Ann Neurol* 1:599–600
3089. Schrell UMH, Gauer S, Kiesewetter F, Bickel A, Hren J, Adams EF, Fahlbusch R (1995) Inhibition of proliferation of human cerebral meningioma cells by suramin: effects on cell growth, cell cycle phases extracellular growth factors and PDGF-BB autocrine growth loop. *J Neurosurg* 82:600–607
3090. Schröder R, Kaess H (1972) Atypischen Mitosen bei menschlichen Hirntumoren (Medulloblastome und Glioblastome). *Acta Neuropathol (Berl)* 20:171–173
3091. Schröder R, Müller W, Bonis G, Vorreith M (1970) Statistische Beiträge zum Grading der Gliome III Astrozytome und Oligodendrogliome. *Acta Neurochir (Wien)* 23:1–29
3092. Schultheiss TE, Elizabeth M, Higgins M, El-Mahdy A (1984) The latent period in clinical radiation myelopathy. *Int J Radiat Oncol Biol Phys* 10:1109–1115
3093. Schultz MD, Wang CC, Zinniger GF, Tefft M (1968) Radiotherapy of intracranial neoplasms. In: Krayenbühl H, Maspes PE, Sweet WH (eds) *Progress in neurological surgery*. Karger, Basel, pp 319–370
3094. Schuman LM, Choi NW, Gullen WH (1967) Relationship of central nervous system neoplasms to toxoplasma gondii infection. *Am J Public Health* 57:848–856
3095. Schwab M (1990) Amplification of the N-myc oncogene and deletion of putative tumour suppressor gene in human neuroblastomas. *Brain Pathol* 1:41–46
3096. Schwartz AM, Ghatak NR, Laine FJ (1990) Intracellular primitive neuroectodermal tumor (PNET) in familial retinoblastoma: a variant of “trilateral retinoblastoma”. *Clin Neuropathol* 9:55–59
3097. Schwartz LM, Smith SW, Jones ME, Osborne BA (1993) Do all programmed cell deaths occur via apoptosis? *Proc Natl Acad Sci. USA* 90:980–984
3098. Schwartz MR, Randolph RL, Cech DA, Rose JE, Panko WB (1984) Steroid hormone binding macromolecules in meningiomas: failure to meet criteria of specific receptors. *Cancer* 53:922–927
3099. Schwartz P, Klauer HR (1927) Diffuse systematische blastomatöse Wucherung des gliöses Apparaten im Gehirn. *Z Ges Neur Psych* 109:438–452
3100. Schwachheimer K, Cavenee WK (1993) Genetics of cancer predisposition and progression. *Clin Invest* 71:488–502
3101. Schwachheimer K, Kühl (1983) Arteriovenous angioma of the vein of Galen causing cardiac failure in the neonate. Report on clinical and pathological findings in two cases. *Neuropediatrics* 14:184–189
3102. Schwachheimer K, Möller P, Schnabel P, Waldherr R (1983) Emphasis on peanut lectin as a marker for granular cells. *Virchows Arch [A] Path Anat His* 399:289–297
3103. Schwachheimer K, Wiedenmann B, Franke WW (1987) Synaptophysin: a reliable marker for medulloblastomas. *Virchows Arch [A] Path Anat His* 411:53–59
3104. Schweigerer L, Neufeld G, Friedman J, Abraham JA, Fiddes JC, Gospodarowicz D (1987) Capillary endothelial cells express basic fibroblast growth factor, a mitogen that promotes their own growth. *Nature* 325:257–259
3105. Schweiki D, Itin A, Soffer D, Keshet E (1992) Vascular endothelial growth factor induced by hypoxia may mediate hypoxia-initiated angiogenesis. *Nature* 359:843–845

3106. Scott M, Bentz R (1962) Intramedullary neurilemmoma (neurinoma) of the thoracic cord. A case report. *J Neuropathol Exp Neurol* 21:194–200
3107. Scott R, Ballantine H (1973) Cerebellar astrocytoma: malignant recurrence after prolonged postoperative survival. *J Neurosurg* 39:777–783
3108. Scott RF, Daoud AS, Wortman B (1966) Proliferation and necrosis in coronary and cerebral arteries. *J Atheroscler Phys* 6:499–509
3109. Scott RM, Barnes P, Kupsky W, Adelman LS (1992) Cavernous angioma of the central nervous system in children. *J Neurosurg* 76:38–46
3110. Scotto KV, Biedler JL, Melera PW (1986) Amplification and expression of genes associated with multidrug resistance in mammalian cells. *Science* 232:751–755
3111. Sedan R (1957) Les néoformations intracrâniennes de l'enfant. Thesis, Aix-en-Provence
3112. Sedzimir CB, Frazer AK, Roberts JR (1973) Cranial and spinal meningiomas in a pair identical twin boys. *J Neurol Neurosurg Psychiatr* 36:368–376
3113. Seeger RC, Brodeur GM, Sather H, Dalton A, Siegel WE, Wong KY, Hammond D (1985) Association of multiple copies of the N-myc oncogene with rapid progression of neuroblastomas. *N Engl J Med* 313:111–116
3114. Seemayer TA, Blunde JS, Wigglesworth FW (1972) Pituitary craniopharyngioma with tooth formation. *Cancer* 29:423–430
3115. Seidman H, Selikoff IJ, Hammond EC (1982) Mortality of brain tumors among asbestos insulation workers in the United States and Canada. *Ann NY Acad Sci* 381:160–171
3116. Seitz RJ, Wechsler W (1986) Vascularization of human cerebral gliomas: a lectin-cytochemical morphometric study. In: Walker MD, Thomas DGT (eds) *Biology of brain tumour*. Nijhoff, Boston, pp 132–137
3117. Seitz RJ, Deckert M, Wechsler W (1988) Vascularization of syngenic intracerebral RG2 and F98 rat transplanted tumors. *Acta Neuropathol (Berl)* 76:599–605
3118. Seizinger BR, Martuza RL, Gusella JF (1986) Loss of genes on chromosome 22 in tumorigenesis of human acoustic neuroma. *Nature* 322:644–647
3119. Seizinger BR, Rouleau G, Ozelius LJ, Lane AH, George-Hyslop PH, Huson S, Gusella JF, Martuza RL (1987) Common pathogenetic mechanism for three tumor types in bilateral acoustic neurofibromatosis. *Science* 236:317–319
3120. Seizinger BR, Rouleau GA, Ozelius LJ, Lane AH, Faryniarz AG, Chao MV, Huson SK, Parry DM, Pericak-Vance MA, Collins FS, Hobbs WJ, Falcone BG, Iannazzi JA, Roy JC, St. George-Hyslop PH, Tanzi RM, Bothwell MA, Upadhyaya M, Harper P, Goldstein AE, Hoover DL, Bader JL, Spence MA, Mulvihill JJ, Aylsworth AS, Vance JM, Rossenwasser GOD, Gaskell PC, Roses AD, Martuza RL, Breakefield XO, Gusella JF (1987) Genetic linkage of von Recklinghausen Neurofibromatosis to the nerve growth factor receptor gene. *Cell* 49:589–594
3121. Seizinger BR, Rouleau GA, Ozelius LJ, Lane LJ, Farmer GE, Lamiell JM, Haines J, Yuen JWM, Collins D, Majoor-Krakauer D, Bonner T, Mathew C, Rubenstein A, Halperin J, McConkie-Rosell A, Green JS, Trofatter JA, Ponder BAJ, Eiermann L, Bowmer MI, Schimke R, Oostra B, Aronin N, Smith DI, Drabkin H, Waziri MH, Hobbs WJ, Martuza RL, Conneally PM, Hsia YE, Gusella JF (1988) Von Hippel-Lindau disease maps to the region of chromosome 3 associated with renal cell carcinoma. *Nature* 332:268–269
3122. Seizinger BR, Smith DL, Filling-Katz MR, Neumann HPH, Green JS, Choyke PL, Anderson KM, Freiman RN, Klauck SM, Whaley J, Decker HJH, Hsia YE, Cllins D, Halperin J, Lamiell JM, Oostra B, Waziri MH, Gorin MB, Scherer G, Drabkin HA, Aronin N, Schinzel A, Martuza RL, Gusella JF, Haines JL (1991) Genetic flanking markers refine diagnostic criteria and provide insights into the genetics of von Hippel-Lindau disease. *Proc Natl Acad Sci USA* 88:2864–2868
3123. Selker RG (1983) Corticosteroids: their effects on primary and metastatic brain tumors. In: Walker MD (ed) *Oncology of the nervous system*. Nijhoff, Boston, pp 167–191
3124. Seloosse MP (1962) Chordome intracrâniennes. Étude d'un cas à forme topographique inférieure. *Neurochirurgie* 8:94–99
3125. Selverstone B, Cooper DR (1961) Astrocytomas and ABO blood groups. *J Neurosurg* 18:602–604
3126. Selye H (1965) *The mast cells*. Butterworths, Washington

3127. Serano RD, Pegram CN, Fraser H, Dickerson AG, Bigner DD (1978) Established tumorigenic cell lines from a spontaneous murine (VM/Dk) astrocytoma (SMA). *J Neuropathol Exp Neurol* 37:689
3128. Seress L (1980) Development and structure of the radial glia in the post-natal rat brain. *Anat Embryol* 160:213–226
3129. Serlenga L, Spina A (1969) Le metastasi endocraniche (Studio clinico-statistico dei casi osservati nel decennio 1958–1967). *Acta Neurol (Napoli)* 24:49–54
3130. Seshi B, True L, Carter D, Rosai J (1988) Immunohistochemical characterization of a set of monoclonal antibodies to human neuron-specific enolase. *Am J Pathol* 131:258–269
3131. Shafit-Zagardo B, Kune-Iwakura A, Goldman JE (1988) Astrocytes regulate GFAP mRNA levels by cyclic AMP and protein kinase C-dependent mechanism. *Glia* 1:346–354
3132. Shanklin WM (1949) On the presence of cysts in the human pituitary. *Anat Rec* 104:379–408
3133. Shanklin WM (1951) The incidence and distribution of cilia in the human pituitary with a description of micro-follicular cysts derived from Rathke's cleft. *Acta Anat Scand* 361–382
3134. Shanklin WM (1953) The origin, histology and senescence of tumorettes in the human neurohypophysis. *Acta Anat* 18:1–19
3135. Shannon KM, O'Connell P, Martin GA, Paderanga D, Olson K, Dinndorf P, McCormick F (1994) Loss of the normal NF1 allele from the bone marrow of children with type 1 neurofibromatosis and malignant myeloid disorders. *N Engl J Med* 330:597–601
3136. Shapiro JR, Schenck AC (1991) Molecular biological events in the selection of chemotherapy resistant-cells in human malignant gliomas. In: Paoletti P, Takakura K, Walker MD, Butti G, Pezzotta S (eds) *Neurooncology*. Kluwer, Dordrecht, pp 21–26
3137. Shapiro JR, Shapiro WR (1984) Clonal tumor cell heterogeneity. *Progr Exp Tumor Res* 27:49–66
3138. Shapiro JR, Yung WKA, Shapiro WR (1981) Isolation, karyotype and clonal growth of heterogeneous subpopulations of human malignant glioma. *Cancer Res* 41:2349–2359
3139. Shapiro K, Till K, Grant N (1979) Craniopharyngiomas in childhood. A rational approach to treatment. *J Neurosurg* 50:617–623
3140. Shapiro S, Maeley J, Sartorius C, (1989) Radiation-induced intracranial malignant gliomas. *J Neurosurg* 71:77–82
3141. Shapiro W, Young D, Mehta B, (1975) Methotrexate: distribution in cerebrospinal fluid after intravenous ventricular and lumbar injections. *N Engl J Med* 293:161–166
3142. Shapiro WR (1989) Recent initiatives in brain tumor therapy. *J Neurooncol* 7:27
3143. Shapiro WR, Byrne TN (1983) Chemotherapy of brain tumors – basic concepts. In: Walker MD (ed) *Oncology of the nervous system*. Nijhoff, Boston, pp 65–100
3144. Shapiro WR, Young DF (1984) Neurological complications of antineoplastic therapy. *Acta Neurol Scand* 70:125–132
3145. Shapiro WR, Ausman JI, Rall DP (1970) Studies on the chemotherapy of experimental brain tumors: development of an experimental model. *Cancer Res* 30:2401–2413
3146. Shapiro WR, Chernik NL, Posner JB (1973) Necrotizing encephalopathy following intraventricular instillation of methotrexate. *Arch Neurol* 28:96–101
3147. Shapiro WR, Basler GA, Chernik NL, Posner JB (1979) Human brain tumor transplantation into nude mice. *J Natl Cancer Inst* 62:447–453
3148. Shapiro WR, Green SB, Burger PC, Mahaley MS, Selker RG, Van Gilder JC, Robertson JT, Ransohoff J, Mealey J, Strike TA, Pistenmaa DA (1989) Randomized trial of three chemotherapy and two radiotherapy regimens in postoperative treatment of malignant glioma. *J Neurosurg* 71:1–9
3149. Shapiro WR, Green SB, Burger PC, Selker RG, Van Gilder JC, Robertson JT, Mealey J Jr, Ransohoff J, Matalley MS (1992) A randomized comparison of intraarterial versus intravenous BCNU, with or without intravenous 5-fluorouracil for newly diagnosed patients with malignant glioma. *J Neurosurg* 76:772–781
3150. Shaw CM, Sumi SM, Alvord EC, Gerdes AJ, Spence A, Parker RG (1978) Fast neutron irradiation of glioblastoma multiforme. Neuropathological analysis. *J Neurosurg* 49:1–12
3151. Shaw EG, Dumas-Duport C, Scheithauer BW, Gilbertson DT, O'Fallon JR, Earle JD, Laws ER Jr, Okazaki H (1989) Radiation therapy in the management of low-grade supratentorial astrocytomas. *J Neurosurg* 70:853–861



3152. Shaw EG, Evans RG, Scheithauer BW (1986) Radiotherapeutic management of adult intraspinal ependymomas. *Int J Radiat Oncol Biol Phys* 12:323–327
3153. Shaw EG, Scheithauer BW, Gilbertson DT, Nichols DA, Laws ER, Earle JD, Dumas-Duport C, O'Fallon JR, Dinapoli RP (1989) Postoperative radiotherapy of supratentorial low-grade gliomas. *Int J Radiat Oncol Biol Phys* 16:663–668
3154. Shaw EG, Scheithauer BW, O'Fallon JR, Tazelaar HD, Davis DH (1992) Oligodendrogliomas: the Mayo Clinic experience. *J Neurosurg* 76:428–434
3155. Shaw E, Farnan M, Souhami L, Dinapoli R, Kline R, Loeffler J, Fisher B (1995) Treatment of previously irradiated recurrent primary brain tumors and brain metastases with radiosurgery: report of Radiation Therapy Oncology Group (RTOG) protocol 90–95. In: *Proceedings of the 11th International Conference on Brain Tumors Research and Therapy*, 31 October–3 November, Silverado, Ca
3156. Shaw E, Scott C, Souhami L, Dinapoli R, Kline R, Loeffler J, Fisher B, Farnan N (1995) RTOG protocol 90–05 radiosurgical treatment of previously irradiated recurrent primary brain tumors and brain metastases final report. In: *Proceedings 11th International Conference on Brain Tumor Research and Therapy*, Silverado, Ca
3157. Sheline GE (1980) Irradiation injury of the human brain: a review of clinical experience. In: Gilbert HA, Kagan AR (eds) *Radiation damage to the nervous system*. Raven, New York, pp 39–58
3158. Shepherd CW, Scheithauer BW, Gomez MR, Altermatt HJ, Katzmann JA (1991) Subependymal giant cell astrocytoma: a clinical, pathological, and flow cytometric study. *Neurosurgery* 28:864–868
3159. Sheppard JR (1972) Difference in the cAMP levels in normal and transformed cell. *Nature* 236:14–16
3160. Sheridan F, Scharf D, Henderson VW, Millar CA (1990) Lipomas of the mesencephalic tectum and rostral pons associated with sleep apnea syndrome. *Clin Neuropathol* 9:152–153
3161. Sherman ME, Erozan YS, Mann RB, Kumar AA, McArthur JC, Royal W, Uematsu S, Nauta HJ et al (1991) Stereotactic brain biopsy diagnosis of malignant lymphoma. *Am J Clin Pathol* 95:878–883
3162. Sherwin RP, Grassi JE, Sommers SC (1962) Hamartomatous malformations of the posterolateral hypothalamus. *Lab Invest* 11:89–97
3163. Shibata S (1989) Sites of origin of primary intracerebral malignant lymphoma. *Neurosurgery* 25:14–19
3164. Shibuya M, Hoshino T, Ito S, Wacker MR, Prados MD, Davis RL, Wilson CB (1992) Meningiomas: clinical implications of a high proliferative potential determined by bromodeoxyuridine labeling. *Neurosurgery* 30:494–498
3165. Shibuya M, Ito S, Miwa T, Davis RL, Wilson CB, Hoshino T (1993) Proliferative potential of brain tumors. Analyses with Ki67 and anti-DNA polymerase alpha monoclonal antibodies, bromodeoxyuridine labeling, and nuclear organizer region counts. *Cancer* 71:199–206
3166. Shibuya M, Ito S, Davis RL, Wilson CB, Hoshino T (1993) A new method analyzing the cell kinetics of human brain tumors by double labeling with bromodeoxyuridine in situ and with iododeoxyuridine in vitro. *Cancer* 71:3109–3113
3167. Shih CJ (1977) Intracranial tumors in Taiwan. A cooperative study of 1200 cases with special reference to the intracranial tumors in children. *J Formosan Med Assoc* 76:515–528
3168. Shimokawa I (1986) Immunohistochemical properties of glial cells of ethylnitrosourea induced brain tumor in the rat. *Acta Med Nagasaki* 31:90–116
3169. Shimura T, Hirano A, Llena JF (1985) Ultrastructure of cerebellar hemangioblastoma. Some new observations on the stromal cells. *Acta Neuropathol (Berl)* 67:6–12
3170. Shin W-Y, Laufer H, Lee Y-C, Aftalion B, Hirano A, Zimmerman HM (1978) Fine structure of a cerebellar neuroblastoma. *Acta Neuropathol (Berl)* 42:11–13
3171. Shinoda J, Niwa Y, Sakai N, Yamada H, Shima H, Kato K, Takahashi M, Shimokawa K (1985) Immunohistochemical study of placental alkaline phosphatase in primary intracranial germ cell tumors. *J Neurosurg* 63:733–739
3172. Shinoda J, Yamada H, Sakai N, Ando T, Hirata T, Hirayama H (1989) Malignant cerebellar astrocytic tumours in children. *Acta Neurochir (Wien)* 98:1–8

3173. Shiraishi T, Tabuchi K, Toda K, Kawaguchi S (1995). Apoptotic cell death and apoptosis-related gene products in brain tumors. *Proc 11th International Conference on Brain Tumor Research and Therapy*, 31 October–3 November, Silverado, Ca
3174. Shore RE, Albert RE, Pasternack BS (1976) Follow-up study of patients treated by x-ray epilation for Tinea capitis: resurvey of post-treatment illness and mortality experience. *Arch Environ Health* 31:21–28
3175. Shore RE, Pasternack BS, Thiessen Ev (1979) A case-control study of hair dye use and breast cancer. *J Natl Cancer Inst* 62:277–283
3176. Short MP, Haines J, Jewell A, Bejjani B, Yang CH, Wyandt H, MacFarlane H, Anderman E, Kwiatkowski DJ, Amos J (1991) Clinical findings and linkage studies in familial tuberous sclerosis. *Ann NY Acad Sci* 615:380–381
3177. Short MP, Martuza RL, Huson SM (1994) Neurofibromatosis 2: clinical features, genetic counselling and management issues. In: Huson SM, Hughes RAC (eds) *The neurofibromatoses: a pathogenetic and clinical overview*. Chapman and Hall, London, pp 414–444
3178. Short MP, Richardson EP Jr, Haines JL, Kwiatkowski DJ (1995) Clinical, neuropathological and genetic aspects of the tuberous sclerosis complex. *Brain Pathol* 5:173–179
3179. Shreekumar S, Rosenbluth PR (1959) Angioinvasive nonchromaffin paraganglioma of the glomus jugulare. *Neurology* 9:298–302
3180. Shuangshoti S (1991) Primary meningiomas outside the central nervous system. In: Al-Mefty O (ed) *Meningiomas*. Raven, New York, pp 107–128
3181. Shuangshoti S, Netsky MG (1966) Histogenesis of the choroid plexus in man. *Am J Anat* 118:283–316
3182. Shuangshoti S, O'Charoen S (1983) Cerebellar neoplasm of mixed mesenchymal and neuroepithelial origin. *J Neurosurg* 59:337–343
3183. Shuangshoti S, Roberts MP, Netsky MG (1965) Neuroepithelial (colloid) cyst. Pathogenesis and relation to choroid plexus and ependyma. *Arch Pathol* 80:214–224
3184. Shuangshoti S, Netsky MG, Nashold BR (1970) Epithelial cysts related to sella turcica. Proposed origin for neuroepithelium. *Arch Pathol* 90:444–450
3185. Shuangshoti S, Phonprasert C, Suwanwela N, Netsky MG (1975) Combined neuroepithelial (colloid) cyst and xanthogranuloma (xanthoma) in the third ventricle. *Neurology* 25:547–552
3186. Shuin T, Kondo K, Torigoe S, Kishida T, Kubota Y, Hosaka M, Nagashima Y, Kitamura H, Latif F, Zbar B (1994) Frequent somatic mutations and loss of heterozygosity of the von Hippel-Lindau tumor-suppressor gene in primary human renal cell carcinomas. *Cancer Res* 54:2852–2855
3187. Shuman RN, Alvord EC, Leech RW (1975) The biology of childhood ependymomas. *Arch Neurol* 32:731–739
3188. Sidman RL, Rakic P (1973) Neuronal migration, with special reference to developing human brain: a review. *Brain Res* 62:1–35
3189. Sidransky D, Mikkelsen T, Schwechheimer K, Rosemblum ML, Cavanee W, Vogelstein B (1992) Clonal expansion of p53 mutant cells is associated with brain tumor progression. *Nature* 355:846–847
3190. Siegal T, Horowitz A, Gabizon A (1995) Doxorubicin encapsulated in sterically stabilized liposomes for the treatment of a brain tumor model: biodistribution and therapeutic efficacy. *J Neurosurg* 83:1029–1037
3191. Silva EG, Butler JJ, Mackay B, Goepfert H (1982) Neuroblastomas and neuroendocrine carcinomas of the nasal cavity: a proposed new classification. *Cancer* 50:2388–2405
3192. Silver JM, Rawlings CE, Rossitch H Jr, Zeidman SM, Friedman AH (1991) Ganglioglioma: a clinical study with long-term follow-up. *Surg Neurol* 35:261–266
3193. Sima AAF, Robertson DM (1979) Subependymal giant-cell astrocytoma. Case report with ultrastructural study. *J Neurosurg* 50:240–245
3194. Sima AAF, Ross R, Hoag G, Rozdilsky B, Diocce M (1988) Malignant intracranial fibrous histiocytoma. Histologic ultrastructural, immunohistochemical studies of two cases. *Can J Neurol Sci* 13:138–145
3195. Simard JM, Garcia-Bengochea F, Ballinger WE Jr, Mickle JP, Quisling RG (1986) Cavernous angioma: a review of 126 collected and 12 new clinical cases. *Neurosurgery* 18:162–172
3196. Simeone A, Acampora D, Gulisano M, Stornaiuolo A, Boncinelli E (1992) Nested expression domains of four homeobox genes in developing rostral brain. *Nature* 358:687–690

3197. Simionescu MD (1960) Metastatic tumors of the brain. A follow-up study of 195 patients with neurosurgical considerations. *J Neurosurg* 17:361–373
3198. Simko TG, Griffin TW, Gerdes AJ (1978) The role of radiation therapy in the treatment of glomus jugulare tumors. *Cancer* 42:104–106
3199. Simon J, Jones EL, Trumper MM, Salmon MV (1987) Malignant lymphomas involving the central nervous system. A morphological and immunohistochemical study of 32 cases. *Histopathology* 11:335–349
3200. Simon T (1874) Das Spinnenzellen- und Pinselzellengliom. *Virchows Arch [A] Path Anat His* 61:90–100
3201. Simpson D (1957) The recurrence of intracranial meningioma after surgical treatment. *J Neurol Neurosurg Psychiatr* 20:22–39
3202. Simpson RHW, Phillips Ji, Miller P, Hagen D, Anderson JEM (1986) Intracerebral malignant fibrous histiocytoma: a light and electron microscopic study with immunohistochemistry. *Clin Neuropathol* 5:185–189
3203. Simpson RK, Brunner JM, Leavens ME (1989) Metastatic Ewing's sarcoma to the brain: case report and review of treatment. *Surg Neurol* 31:234–238
3204. Simson LR, Lampe I, Abell MR (1968) Suprasellar germinomas. *Cancer* 22:533–544
3205. Singer M, Nordlander RH, Egar M (1979) Axonal guidance during embryogenesis and regeneration in the spinal cord of the newt: the blueprint hypothesis of neuronal pathway patterning. *J Comp Neurol* 185:1–22
3206. Singh A, Stobos RJ, Singh BM, Rothbaler AB, Reddy V, Puljic S, Poon TP (1982) Steroid-induced remissions in CNS lymphoma. *Neurology* 32:1267–1271
3207. Siqueira EB, Kanaan I, Ali A (1989) Large meningioma of the foramen magnum in a 4-year-old child. *Surg Neurol* 31:409–411
3208. Sjögren HO, Ellstrom J, Bansal SC (1971) Suggestive evidence that "blocking antibodies" of tumor-bearing individuals may be antigen-antibody complexes. *Proc Natl Acad Sci USA* 68:1372–1375
3209. Skala O (1956) Über ein extraventrikuläres Plexuspapillom. *Zbl allg Path Anat* 95:183–187
3210. Skalski V, Feindel W, Panasci LC (1990) Transport of amino acid amide sarcosinamide and sarcosinamide chloroethylnitrosourea in human glioma SK-MG-1 cells. *Cancer Res* 50:3062–3066
3211. Skapek SX, Colvin OM, Griffith OW, Groothuis DR, Colapinto EV, Lee Y, Hilton J, Elion GB, Bigner DD, Friedman HS (1988) Buthionine sulfoximine-mediated depletion of glutathione in intracranial human glioma-derived xenografts. *Biochem Pharmacol* 37:4313–4317
3212. Skelton III H, Smith K, Barrett T et al (1991) HMB 45 staining in benign and malignant melanocytic lesions. *Am J Dermatopathol* 13:543–550
- 3212a. Sklar CA, Constine LS (1995) Chronic neuroendocrinological sequelae of radiation therapy. *Int J Radiat Biol Phys* 31:1113–1121
3213. Skoff RP, Price DL, Stocks A (1976) Electron microscopic autoradiographic studies of gliogenesis in rat optic nerve. 1. Cell proliferation. *J Comp Neurol* 169:291–312
3214. Skullerud K, Löken AC (1974) The prognosis in meningiomas. *Acta Neuropathol (Berl)* 29:337–334
3215. Skultety FM, Sorrel MF, Burklund CW (1970) Hemangioblastoma of the cerebellum associated with erythrocytosis and an unusual blood supply. Case report. *J Neurosurg* 32:700–705
3216. Skuse GR, Kosciolk BA, Rowley PT (1991) The neurofibroma in von Recklinghausen neurofibromatosis has a unicellular origin. *Am J Hum Genet* 49:600–607
3217. Skuse GR, Ludlow JW (1995) Tumor suppressor genes in disease and therapy. *Lancet* 345:902–906
3218. Slager UT, Kaufman RL, Cohen KL, Tuddenham WJ (1982) Primary lymphoma of the spinal cord. *J Neuropathol Exp Neurol* 41:437–445
3219. Slamon DJ, Cline MJ (1984) Expression of cellular oncogenes during embryonic fetal development of the mouse. *Proc Natl Acad Sci USA* 81:7141–7145
3220. Slifkin M, Merkow LP, Pardo M, Rapoza NP (1969) Oncogenic Simian adenoviruses. V. Recovery of infectious virus from intracranial tumor cells induced by Simian adenovirus 7. *J Natl Cancer Inst* 43:423–435
3221. Slooff JL, Kernohan JW, MacCarty CS (1964) Primary intramedullary tumors of the spinal cord and filum terminale. Saunders, Philadelphia

3222. Slowik F, Balogh I (1980) Extracranial spreading of glioblastoma multiforme. *Zbl Neurochir* 41:57–68
3223. Slowik F, Jellinger K (1990) Association of primary cerebral lymphoma with meningioma: a report of 2 cases. *Clin Neuropathol* 9:69–73
3224. Slowik F, Jellinger K, Gaszo L, Fischer J (1985) Gliosarcomas: histological, immunohistochemical, ultrastructural, and tissue culture studies. *Acta Neuropathol (Berl)* 67:201–210
3225. Small RK, Riddle P, Noble M (1987) Evidence for migration of oligodendrocyte-type 2 astrocyte progenitor cells into developing rat optic nerve. *Nature* 328:155–157
3226. Smaltino F, Cucciniello B (1968) Epidermoid tumor of the epiphysial region. *J Neurosurg* 28:63–66
3227. Smart I (1961) The subependymal layer of the mouse brain and its cell production as shown by radioautography after thymidine-H3 injection. *J Comp Neurol* 116:325–347
3228. Smart I (1965) The operation of ependymal “choke” in neurogenesis. *J Anat* 99:941–948
3229. Smart I, Leblond CP (1961) Evidence for division of neuroglia cells in the mouse brain, as derived from radioautography after injection of Thymidine-H3. *J Comp Neurol* 116:349–367
3230. Smith DA, Lantos PL (1985) Immunocytochemistry of cerebellar astrocytomas with a special note on Rosenthal fibres. *Acta Neuropathol (Berl)* 66:155–159
3231. Smith KR Jr, Schwartz MG, Luse SA, Ogura JM (1963) Nasal gliomas. A report of five cases with electron microscopy of one. *J Neurosurg* 20:968–982
3232. Smith MT, Ludwig CL, Godfrey AD, Armbrustmacher VW (1983) Grading of oligodendrogliomas. *Cancer* 52:2107–2114
3233. Smith TW, Bhawan J (1980) Tactile-like structures in neurofibromas. An ultrastructural study. *Acta Neuropathol (Berl)* 50:233–236
3234. Smith TW, Davidson RI (1984) Medulloblastoma: a histologic, immunohistochemical and ultrastructural study. *Cancer* 54:323–332
3235. Smith TW, Nikulasson S, De Girolami U, De Gennaro LJ (1993) Immunohistochemistry of synapsin I and synaptophysin in human nervous system and neuroendocrine tumors. *Clin Neuropathol* 6:335–342
3236. Sneed PK, Prados MD, McDermott MW, Larson DA, Malec MK, Lamborn KR, Davis RL, Weaver KA, Wara WM, Phillips TL, Gutin PH (1995) Large effect of age on the survival of patients with glioblastoma treated with radiotherapy and brachytherapy boost. *Neurosurgery* 36: 898–904
3237. Sneed PK, Shiau C-Y, Shu H-KG, Wara WM, Petti PL, Smith V, Verhey LJ, McDermott MW, Nowak P, Gutin PH, Larson DA (1995) Results of gamma knife radiosurgery for single and multiple brain metastases. In: 11th International Conference on Brain Tumor Research and Therapy, 31 October–3 November, Silverado, Ca
3238. Snell KG, Stewart HL, Morris MP, Wagner BP, Ray FE (1961) Intracranial neurilemmoma and medulloblastoma induced in rats by the dietary administration of N,N'-2,7-fluorenylenibisacetamide. *Nat Cancer Inst Monogr* 5:85–103
3239. Snider WD, Simpson DM, Nielsen S, Gold JWM, Metroka CE, Posner JB (1983) Neurological complications of acquired immune deficiency syndrome: analysis of 50 patients. *Ann Neurol* 14:403–418
3240. Snipes GJ, Steinberg GK, Lane B, Horonpian DS (1991) Gliofibroma. Case report. *J Neurosurg* 75:642–646
3241. So NK, O'Neill BP, Frytak S, Eagan RT, Earnest IV F, Lee RE (1987) Delayed leukoencephalopathy in survivors with small cell lung cancer. *Neurology* 37:1198–1201
3242. So YT, Beckstead JH, Davis RL (1986) Primary central nervous system lymphoma in acquired immune deficiency syndrome: a clinical and pathology study. *Ann Neurol* 20:566–572
3243. Sobel RA, Wang Y (1993) Vestibular (acoustic) Schwannomas: histological features in Neurofibromatosis 2 and in unilateral cases. *J Neuropathol Exp Neurol* 52:106–113
3244. Sobel RA, Trice JE, Nielsen SL, Ellis WG (1981) Pineoblastoma with ganglionic and glial differentiation: report of two cases. *Acta Neuropathol (Berl)* 55:243–246
3245. Soffer D, Pittaluga S, Feiner M, Belber AJ (1983) Intracranial meningiomas following low-dose irradiation to the head. *J Neurosurg* 59:1048–1053
3246. Soffer D, Gomori M, Siegal T, Shalit M (1989) Intracranial meningiomas after high dose irradiation. *Cancer* 63:1514–1519

3247. Soffer D, Gomori JM, Pomeranz S, Siegal T (1990) Gliomas following low-dose irradiation to the head: report of three cases. *J Neurooncol* 8:67–72
3248. Soffietti R, Chiò A (1989) Prognostic factors in cerebral astrocytic gliomas. In: Broggi G, Gerosa MA (eds) *Cerebral gliomas*. Elsevier, Amsterdam, pp 149–150
3249. Soffietti R, Sciolla R, Giordana MT, Vasario E, Schiffer D (1985) Delayed adverse effects after irradiation of gliomas: clinicopathological analysis. *J Neurooncol* 3:187–192
3250. Soffietti R, Chiò A, Giordana MT, Vasario E, Schiffer D (1988) Anaplastic astrocytomas: prognostic value of histologic features and their relationship with clinico-therapeutic factors. *Clin Neuropathol* 7:211
3251. Soffietti R, Chiò A, Giordana MT, Vasario E, Schiffer D (1989) Prognostic factors in well-differentiated cerebral astrocytomas in the adult. *Neurosurgery* 24:686–692
3252. Soffietti R, Chiò A, Mocellini C, Rudà R, Schiffer D (1995) Treatment with carboplatinum on oligodendroglial tumors recurrent after PCV chemotherapy. *Neurology* 45 [Suppl 4] A 261, 365
3253. Sogg RL, Donaldson SS, Yorke CH (1978) Malignant astrocytoma following radiotherapy of a craniopharyngioma. *J Neurosurg* 48:622–627
3254. Soini Y, Niemela A, Kamel D, Herva R, Bloigu R, Paakko P, Vahakangas K (1994) p53 immunohistochemical positivity as a prognostic marker in intracranial tumors. *APMIS* 102:786–792
3255. Sokoloff L, Reivich M, Kennedy C, Des Rosiers MH, Patlak CS, Pettigrew KD, Sakurada O, Shinohara M (1977) The (14C) deoxyglucose method for the measurement of local cerebral glucose utilization: Theory, procedure, and normal values in the conscious and anesthetized albino rat. *J Neurochem* 28:897–916
3256. Soleman M (1995) Experimental therapy for brain tumors. In: *Brain Tumors*. Kaye AM, Laws ER (eds) Churchill Livingstone, New York, pp 369–385
3257. Solero CL, Fornari M, Giombini S, Lasio G, Oliveri G, Cimino C, Pluchino F (1989) Spinal meningiomas: review of 174 operated cases. *Neurosurgery* 25:153–160
3258. Solitare GB (1962) Cerebellar and cerebral gliomas occurring in the same individual. *J Neurosurg* 19:1079–1084
3259. Solitare GB, Krigman MR (1964) Congenital intracranial neoplasm. A case report and review of the literature. *J Neuropathol Exp Neurol* 23:280–292
3260. Somogyi P, Hodgson AJ, DeP Potter RW, Fischer-Colbrie R, Schober M, Winkler H, Chubb IW (1984) Chromogranin immunoreactivity in the central nervous system. Immunochemical characterization, distribution and relationship to catecholamine and enkephaline pathways. *Brain Res* 8:193–230
3261. Sonneland PRL, Scheithauer BW, Onofrio BM (1985) Mixopapillary ependymoma. *Cancer* 56:310–317
3262. Sonneland PR, Scheithauer BW, Le Chago J, Crawford BG, Onofrio BM (1986) Paraganglioma of the cauda equina region. Clinicopathologic study of 31 cases with special reference to immunocytology and ultrastructure. *Cancer* 58:1720–1735
3263. Spaar FW, Blech M, Ahyai A (1986) DNA-flow fluorescence-cytometry of ependymomas. Report on ten surgically removed tumours. *Acta Neuropathol (Berl)* 69:153–160
3264. Spallone A, Pastore FS, Giuffrè R, Guidetti B (1990) Choroid plexus papillomas in infancy and childhood. *Childs Nerv Syst* 6:71–74
3265. Sparrow GE, Rubens RD (1981) Brain metastases from breast cancer: clinical course, prognosis and influence of treatment. *J Clin Oncol* 7:291–296
3266. Spaun E, Midholm S, Pedersen NT, Ringsted J (1985) Primary malignant lymphoma of the central nervous system. *Surg Neurol* 24:646–650
3267. Specht CS, Smith TW, De Girolami U, Price JM (1986) Myxopapillary ependymoma of the filum terminale. A light and electron microscopy study. *Cancer* 58:310–317
3268. Spector G, Compagno J, Perez C, Maisel R, Ogura J (1975) Glomus jugulare tumors: effects of radiotherapy. *Cancer* 35:1316–1321
3269. Spelsberg TC, Grahah ML II, Berg NJ, Omehara T, Riehl E, Coulam CB, Ingle JN (1987) A nuclear finding assay to assess the biological activity of steroid receptors in isolated animal and human tissues. *Endocrinology* 121:631–644
3270. Spence AM, Geraci JP (1981) Combined cyclotron fast-neutron and BCNU therapy in a rat brain-tumor model. *J Neurosurg* 54:461–468

3271. Spence AM, Rubinstein LJ (1975) Cerebellar capillary hemangioblastoma. Its histogenesis studied by organ culture and electron microscope. *Cancer* 35:326–341
3272. Spence AM, Geraci JP, Cent RR (1985) Irradiation and BCNU effects in the stroma in a rat trasplanted glioma model: analysis of cerebral tumor bed effect. *Neuropath Appl Neurobiol* 11:229–244
3273. Spence AM, Edmondson SW, Krohn KA, Grundbaum Z, Rasey JS, Steele JE (1986) Toxicity and biodistribution of the radioprotectors WR-2721, WR-77913, and WR-3689 in the CNS following intraventricular or intracisternal administration. *Int J Radiat Oncol Biol Phys* 12:1653–1660
3274. Spence AM, Graham MM, O’Gorman LA, Muri M, Abbott JL, Lewellen TK (1987) Regional blood-to-tissue transport in an irradiated rat glioma model. *Radiat Res* 111:225–236
3275. Spence AM, Rasey JS, Dwyerhansen L, Grunbaum Z, Livesey J, Chin L, Nelson N, Stein D, Krohn KA, Aliosman F (1995) Toxicity, biodistribution and radioprotective capacity of L-homocysteine thiolactone in CNS tissues and tumors in rodents: comparison with prior results with phosphorothioates. *Radiother Oncol* 35:216–226
3276. Spencer CD, Weiss RB, van Eys J, Cohen P, Edwards B (1984) Medulloblastoma metastatic to the marrow. Report of four cases and review of the literature. *J Neurooncol* 2:223–235
3277. Sperner J, Gottschalk J, Neumann K, Schörner W, Lanksch WR, Scheffner D (1994) Clinical, radiological and histological findings in desmoplastic infantile ganglioglioma. *Child’s Nerv Syst* 10:458–463
3278. Speth RC, Harik SI (1985) Angiotensin II receptor binding sites in brain microvessels. *Proc Natl Acad Sci USA* 82:6340–6343
3279. Spitz MR, Johnson CC (1985) Neuroblastoma and paternal occupation: a case-control analysis. *Am J Epidemiol* 121:924–929
3280. Stallcup WB, Beasley L (1987) Bipotential glial precursor cells of the optic nerve express the NG2 proteoglycan. *J Neurosci* 7:2737–2744
3281. Stam FC, Kamphorst W (1982) Echordosis physaliphora as a cause of fatal pontine hemorrhage. *Eur Neurol* 21:90–93
3282. Stam FC, van Alphen HAM, Boorsma DM (1980) Meningioma with conspicuous plasma cell components. A histopathological and immunohistochemical study. *Acta Neuropathol (Berl)* 49:241–243
3283. Stammli A, Marguth E, Schmidt-Wittkamp E (1964) Die Meningitis carcinomatosa und sarcomatosa. *Fortschr Neurol Psychiatr* 32:53–77
3284. Stansfeld A, Diebold J, Noel H, Kpanci Y, Rilke F, Kelényi G, Sundstrom C, Lennert K, van Unnik J, Mioduszezka O, Wright D (1988) Updated Kiel classification for lymphomas. *Lancet* 6:292–293
3285. Stanton C, Perentes E, Collins VP, Rubinstein LJ (1987) GFA protein reactivity in nerve sheath tumors. A polyvalent and monoclonal antibody study. *J Neuropathol Exp Neurol* 46:634–643
3286. Stavrou D, Anzil AP, Weidenbach W, Rodt H (1977) Immunofluorescence study of lymphocytic infiltration in gliomas. Identification of T lymphocytes. *J Neurol Sci* 33:275–282
3287. Steck PA, Ligon AH, Cheong P, Yung WKA, Pershose MA (1995) Two tumor suppressive loci on chromosome 10 involved in human glioblastomas. *Genes Chrom Cancer* 12:255–261
3288. Steegman AT (1971) Chordomas. In: Minckler J (ed) *Pathology of the nervous system*. vol 2, McGraw-Hill, New York, pp 1917–1927
3289. Steel GG (1977) *Growth kinetics of tumours*. Oxford University Press, Clarendon
3290. Stefanko SZ, Mackay WM (1981) Papillary meningioma. *Acta Neuropathol (Berl) Suppl* 7:126–128
3291. Stefanko SZ, Manschot WA (1979) Pinealoblastoma with retinomatous differentiation. *Brain* 102:321–332
3292. Stefanko SZ, Vurevski VD, Maas AIR, van Vroonhoven CCJ (1986) Intracerebral malignant Schwannoma. *Acta Neuropathol (Berl)* 71:321–325
3293. Stefansson K, Wolmann R (1981) Distribution of the neuronal specific protein, 14-3-2, in central nervous system lesions of tuberous sclerosis. *Acta Neuropathol (Berl)* 53:113–117
3294. Stefansson K, Wollmann R, Jerkovic M (1982) S-100 protein in soft tissue tumors derived from Schwann cells and melanocytes. *Am J Pathol* 106:261–268

3295. Stein AA, Schilp AO, Whitfield RD (1960) The histogenesis of hemangioblastoma of the brain. A review of twenty-one cases. *J Neurosurg* 17:751-761
3296. Stein BM (1979) Supracerebellar-infratentorial approach to pineal tumors. *Surg Neurol* 11:331-337
3297. Stein H, Kaiserling E, Lennert K (1974) Evidence for B-cell origin of reticulum cell sarcoma. *Virchows Arch [A] Path Anat His* 364:51-67
3298. Stein MB, Leeds NE, Taveras JM, Pool JL (1963) Meningiomas of the foramen magnum. *J Neurosurg* 20:740-751
3299. Stein M, Haim N, Ben-Shachar M, Goldsher D, Bernstein Z, Ben-Arich Y, Kuten A (1995) Radiation-induced primary brain lymphoma: a case report. *Tumori* 81:204-207
3300. Steinberg GK, Koenig GH, Golden JB (1982) Symptomatic Rathke's cleft cysts. *J Neurosurg* 56:290-295
3301. Steinberg GK, Shuer LM, Conley FK, Hambery JW (1985) Evolution and outcome in malignant astroglial neoplasms of the cerebellum. *J Neurosurg* 62:9-17
3302. Steinbock P, Mahaley S, Zinn DC, Lipper S, Mahaley JL, Bigner DD (1979) Synergism between BCNU and irradiation in the treatment of anaplastic gliomas. An in vivo study using the avian sarcoma virus-induced glioma model. *J Neurosurg* 51:581-586
3303. Steinbock P, Mahaley S, Varia MA, Lipper S, Mahaley J, Dalzell JG, Bigner DD (1980) Treatment of autochthonous rat brain tumors with fractionated radiotherapy. The effects of graded radiation doses and of combined therapy with BCNU or steroids. *J Neurosurg* 53:68-72
3304. Steinsvåg SK, Laerum OD (1985) Transmission electron microscopy of cocultures between normal rat brain tissue and rat glioma cells. *Anticancer Res* 5:137-146
3305. Steinsvåg SK, Laerum OD, Bjerkvig R (1985) Interaction between rat glioma cells and normal rat brain tissue in organ culture. *J Natl Cancer Inst* 74:1095-1104
3306. Stensaas LJ, Stensaas SS (1968) Light microscopy of glial cells in turtles and birds. *Z Zellforsch* 91:315-340
3307. Sternberger LA, Sternberger NH (1983) Monoclonal antibodies distinguish phosphorylated and nonphosphorylated forms of neurofilaments in situ. *Proc Natl Acad Sci USA* 80:6126-6130
3308. Sternberger NH, Itoyama Y, Kies MW, Webster HF (1978) Immunocytochemical method to identify basic protein in myelin-forming oligodendrocytes of newborn rat CNS. *J Neurocytol* 7:251-263
3309. Sternberger NH, Itoyama Y, Kies MW, Webster HF (1978) Myelin basic protein demonstrated immunocytochemically in oligodendroglia prior to myelin sheath formation. *Proc Natl Acad Sci USA* 75:2521-2524
3310. Stetler-Stevenson WG, Brown PD, Onisto M, Levy AT, Liotta LA (1990) Tissue inhibitor of metalloproteinases-2 (TIMP-2) mRNA expression in tumor cell lines and human tumor tissues. *J Biol Chem* 265:13933-13938
3311. Stevenson L, Echlin R (1934) The nature and origin of some tumors of the cerebellum (medulloblastoma). *Arch Neurol Psychiatr* 31:93-109
3312. Steward O, Torre ER, Tomasulo R, Lothman E (1991) Neuronal activity up-regulates astroglial gene expression. *Proc Natl Acad Sci USA* 88:6819-6823
3313. Stewart DJ (1984) Novel modes of chemotherapy administration. *Prog Exp Tumor Res* 28:32-50
3314. Stewart JF, King RJ, Sexton S, Millis RS, Rubens RD, Hayward J (1981) Oestrogen receptors, sites of metastatic disease and survival in recurrent breast cancer. *Eur J Cancer* 17:449-453
3315. Stewart PA, Hayakawa K, Farrell CL, Del Maestro RF (1987) Quantitative study of microvessel ultrastructure in human peritumoral brain tissue. Evidence for a blood-brain barrier defect. *J Neurosurg* 67:697-705
3316. Stoier M (1965) Metastatic tumors of the brain. *Acta Neurol Scand* 41:262-278
3317. Stookey B (1927) Intradural spinal lipoma. Report of a case and symptoms for ten years in a child aged eleven; review of the literature. *Arch Neurol Psychiatry* 18:16-29
3318. Storrer FK, Duguid JB (1954) The vascular formations in glioblastoma. *J Pathol Bacteriol* 68:231-242
3319. Stough DR, Hartzon JT, Fischer RG (1971) Unusual intradural spinal metastasis of a cranial chordoma. Case report. *J Neurosurg* 34:560-562

3320. Stout AP (1935) The peripheral manifestations of the specific nerve sheath tumor (neurilemmoma). *Am J Cancer* 24:751–796
3321. Stöwsand D (1975) Multiple meningiomas. *Acta Neurochir (Wien)* 31:279–286
3322. Strang RR, Höjeberg S, Nordenstam H (1962) Chondrosarcoma of the occipito-cervical region producing a Jackson syndrome. *Zbl Neurochir* 22:36–43
3323. Stratton MR, Darling J, Lantos PL, Cooper CS, Reeves BR (1989) Cytogenetic abnormalities in human ependymomas. *Int J Cancer* 44:579–581
3324. Strauss I, Globus JH (1918) Spongioblastoma with unusually rapid growth following decompression. *Neurol Bull* 1:273–279
3325. Stroebe H (1895) Über Entstehung und Bau der Hirngliome. *Beitr path Anat (Jena)* 18:405–486
3326. Stroink AR, Hoffman HJ, Hendrick EB, Humphreys RP (1986) Diagnosis and management of pediatric brain-stem gliomas. *J Neurosurg* 65:745–750
3327. Strom HE, Skullerud K (1983) Pleomorphic xanthoastrocytoma: report of 5 cases. *Clin Neuropathol* 2:188–191
3328. Strong AJ, Symon L, Mc Gregor BJL, O'Neill BP (1976) Coincidental meningioma and glioma. Report of two cases. *J Neurosurg* 45:455–458
3329. Strouj NE, Blair A, Erickson GE (1986) Brain cancer and other causes of death in anatomists. *J Natl Cancer Inst* 77:1217–1221
3330. Strugar J, Rothbart D, Harrington W, Criscuolo GR (1994) Vascular permeability factor in brain metastases: correlation with vasogenic brain edema and tumor angiogenesis. *J Neurosurg* 81:560–566
3331. Sturrock RR (1975) A light and electron microscopic study of proliferation and maturation of fibrous astrocytes in the optic nerve of the human embryo. *J Anat* 119:223–234
3332. Sturrock RR (1976) Light microscopic identification of immature glial cells in semithin sections of the developing mouse corpus callosum. *J Anat* 122:521–537
3333. Sturrock RR (1979) A quantitative lifespan study of changes in cell number, cell division and cell death in various regions of the mouse forebrain. *Neuropathol Appl Neurobiol* 5:433–456
3334. Sturrock RR (1981) An electron microscopic study of the development of the ependyma of the central canal of the mouse spinal cord. *J Anat* 132:119–136
3335. Sturrock RR (1982) Cell division in the normal central nervous system. In: Fedoroff S, Hertz L (eds) *Advances in cellular neurobiology*, vol 3. Academic, New York, pp 3–33
3336. Sturrock RR, Smart JHM (1980) A morphological study of mouse subependymal layer from embryonic life to old age. *J Anat* 130:391–416
3337. Sugita Y, Kepes JJ, Shigemori M, Kuramoto S, Reifenberger G, Kiwitt JCW, Wechsler W (1990) Pleomorphic xanthoastrocytoma with desmoplastic reaction: angiomatous variant (report of 2 cases). *Clin Neuropathol* 9:271–278
3338. Sukumar S, Barbacic M (1990) Specific patterns of oncogene activation in trasplacentally induced tumors. *Proc Natl Acad Sci USA* 87:718–722
3339. Sumaya C, Boswell R, Ench Y, Kisner D, Hersh E, Reuben J, Mansell P (1986) Enhanced serological and virological findings of Epstein-Barr virus in patients with AIDS and AIDS-related complex. *J Infect Dis* 154:864–870
3340. Sun ZM, Genka S, Shitara N, Akanuma A, Takakura K (1988) Factors possibly influencing the prognosis of oligodendroglioma. *Neurosurgery* 22:886–891
3341. Sundaresan N, Galicich JH, Chu FCH, Huvos AG (1979) Spinal chordomas. *J Neurosurg* 50:312–319
3342. Sundaresan N, Galicich JH, Deck MDF, Tomita T (1981) Radiation necrosis after treatment of solitary intracranial metastases. *Neurosurgery* 8:329–333
3343. Sung JH, Master AR, Segal EL (1973) Melanotic medulloblastoma of the cerebellum. *J Neuropathol Exp Neurol* 32:437–445
3344. Sutherland GR, Florell R, Lome D, Choi NW, Sima AAF (1987) Epidemiology of primary intracranial neoplasms in Manitoba, Canada. *Canad J Neurol Sci* 14:586–592
3345. Sutton LN, Packer LJ, Rorke LB, Bruce DA, Schut L (1983) Cerebral gangliogliomas during childhood. *Neurosurgery* 13:124–128
3346. Suzuki F, Handa J, Todo G (1989) Intracranial glossopharyngeal neurinomas. Report of two cases with special emphasis on computed tomography and magnetic resonance imaging findings. *Surg Neurol* 31:390–394



3347. Suzuki Y, Suzuki H, Kayama T, Toshimoto T, Shibahara S (1991) Brain tumors predominantly express the neurofibromatosis type I gene transcripts containing the 63 base insert in the region coding for GTPase activating protein-related domain. *Biochem Biophys Res Commun* 181:955–961
3348. Svien HJ, Gates EM, Kernohan JW (1949) Spinal subarachnoid implantation associated with ependymoma. *Arch Neurol Psychiatry* 62:847–856
3349. Svien HJ, Mabon RF, Kernohan JW, McK Craig W (1953) Ependymoma of the brain: pathologic aspects. *Neurology* 3:1–15
3350. Svoboda DJ (1959) Oligodendroglioma in a six-week-old infant. *J Neuropathol Exp Neurol* 18:569–574
3351. Swanson PE, Lillemoe TJ, Manivel JC, Wick MR (1990) Mesenchymal chondrosarcoma: an immunohistochemical study. *Arch Pathol Lab Med* 114:943–948
3352. Sweet MBE, Thomas E, Berson SD, Skikne MI, Immelman AR, Kerr WA (1979) Biochemical studies of the matrix of craniovertebral chordoma and a metastasis. *Cancer* 44:652–660
3353. Sweet WH (1976) Radical surgical treatment of craniopharyngioma. *Clin Neurosurg* 23:52–79
3354. Swenberg JA, Wechsler W, Koestner A (1971) The sequential development of transplacentally induced neuroectodermal tumors. *J Neuropathol Exp Neurol* 30:202–203
3355. Swenberg JA, Koestner A, Wechsler W (1972) The induction of tumours of the nervous system with intravenous methylnitrosourea. *Lab Invest* 26:74–85
3356. Swenberg JA, Clendenon N, Denlinger R, Gordon WA (1975) Sequential development of ethylnitrosourea-induced neurinomas: morphology, biochemistry, and transplantability. *J Natl Cancer Inst* 55:147–152
3357. Symeonidis A (1954) Tumours induced by 2-acetylaminofluorene in virgin and breeding females of five strains of rats and in their offsprings. *J Nat Cancer Inst* 15:539–549
3358. Symon L, Sprich W (1985) Radical excision of craniopharyngioma. Results in 20 patients. *J Neurosurg* 62:174–181
3359. Syndikus I, Tait D, Ashley, Jannoun L (1994) Long-term follow-up of young children with brain tumors after irradiation. *Int J Radiat Oncol Biol Phys* 30:4 781–787
3360. Szekely L, Selivanova G, Magnusson K, Klein G, Wiman K (1993) EBNA-5, an Epstein-Barr virus-encoded nuclear antigen, binds to the retinoblastoma and p53 proteins. *Proc Natl Acad Sci USA* 90:5455–5459
3361. Szikla G, Peragut JC (1975) Irradiation interstitielle des gliomes. *Neurochirurgie* 21 [Suppl 2]:187–228
3362. Szikla G, Schlienger M, Blond S, Daumas-Duport C, Missir O, Miyhara S, Musolino A, Schaub C (1984) Interstitial and combined interstitial and external irradiation of supratentorial gliomas. Results in 61 cases treated 1973–1981. *Acta Neurochir (Wien)* 33:355–362
3363. Szymas J, Reifenberger G, Wechsler W (1987) Leu-M1 immunoreactivity in the human brain. Discrimination between different tumors and between neoplastic and brain tissue. *Naturwissenschaften* 74:188–190
3364. Tabuchi H, Nishimoto A, Matsumoto K, Sato T, Nakasone S, Fujiwara T, Ogura H (1985) Establishment of a brain tumor model in adult monkeys. *J Neurosurg* 63:912–916
3365. Tabuchi K, Kirsch WM (1975) Immunocytochemical localization of S-100 in neuron and glia of hamster cerebellum. *Brain Res* 92:175–180
3366. Tabuchi K, Yamada O, Nishimoto A (1973) The ultrastructure of pinealomas. *Acta Neuropathol (Berl)* 27:139–151
3367. Tabuchi K, Moriya J, Furuta T, Ohnishi R, Nishimoto A (1982) S 100 protein in human glial tumours. Qualitative and quantitative study. *Acta Neurochir (Wien)* 65:239–251
3368. Tachibana O, Nakazawa H, Lampa J, Watanabe K, Kleihues P, Ohgaki H (1995) Expression of Fas/APO.1 during the progression of astrocytoma. *Proc 11th Intern Conf Brain Tumor Research and Therapy*, 31 October–3 November, Silverado, Ca
3369. Taghian A, Dubois W, Budach W, Baumann M, Freeman J, Suit H (1995) In vivo radiation sensitivity of glioblastoma multiforme. *Int J Radiat Oncol Biol Phys* 32:99–104
3370. Tait DM, Thornton-Jones J, Bloom HJG, Lemerle J, Morris-Jones P (1990) Adjuvant chemotherapy for medulloblastoma: the first multicentre control trial of the International Society of Paediatric Oncology (SIOP I). *Eur J Cancer* 26:464–469
3371. Takahashi H, Nakazawa S, Shimura T (1985) Evaluation of postoperative intratumoral injection of bleomycin for craniopharyngioma in children. *J Neurosurg* 62:120–127

3372. Takahashi H, Ohara S, Yamada M, Ikuta F, Tanimura K, Honda Y. (1987) Esthesioneuroepithelioma: a tumor of true olfactory epithelium origin. An ultrastructural and immunohistochemical study. *Acta Neuropathol (Berl)* 75:147-155
3373. Takahashi H, Wakabayashi K, Kawai K, Ikuta F, Tanaka R, Takeda N, Washiyama K (1989) Neuroendocrine markers in central nervous system neuronal tumors (gangliocytoma and ganglioglioma). *Acta Neuropathol (Berl)* 77:237-243
3374. Takahashi JA, Mori H, Fujimoto M (1990) Gene expression of fibroblast growth factors in human gliomas and meningiomas: demonstration of cellular source of basic fibroblast growth factor mRNA and peptide in tumor tissues. *Proc Nat Acad Sci USA* 87:5710-5714
3375. Takahashi K, Isobe T, Ohtsuki Y, Akagi T, Sonobe H, Okuyama T (1984) Immunohistochemical study of the distribution of a e b subunits of S-100 protein in human neoplasms and normal tissues. *Virchows Arch [B] Cell Path* 45:385-396
3376. Takakura K, Sano K, Hojo S, Hirano A (1982) Metastatic tumors of the central nervous system. New York, Igaku-Shoin Medical Publisher, Inc
3377. Takamiya Y, Kohsaka S, Taya S, Otanu M, Tsukada Y (1988) Immunohistochemical studies on the proliferation of reactive astrocytes and the expression of cytoskeletal proteins following brain injury in rats. *Dev Brain Res* 38:201-210
3378. Takei Y, Pearl GS (1981) Ultrastructural study of intracranial yolk sac tumor: with special reference to the oncologic phylogeny of germ cell tumors. *Cancer* 48:2038-2046
3379. Takeuchi J, Barnard RO (1976) Perivascular lymphocytic cuffing in astrocytomas. *Acta Neuropathol (Berl)* 35:265-271
3380. Takeuchi K, Hoshino K (1977) Statistical analysis of factors affecting survival after glioblastoma multiforme. *Acta Neurochir (Wien)* 37:57-73
3381. Tamaki N, Lin T, Shirataki K, Hosoda K, Kurata H, Matsumoto S, Ito H (1990) Germ cell tumors of the thalamus and the basal ganglia. *Childs Nerv Syst* 6:3-7
3382. Tamura M, Kawafuchi J, Inone H, Takada F (1979) Prognosis in meningioma after surgical treatment. *Neurol Med Chir (Tokyo)* 19:411-419
3383. Tanaka J, Garcia JH, Netsky MG, Williams JP (1975) Late appearance of meningioma at the site of partially removed oligodendroglioma. *J Neurosurg* 43:80-85
3384. Tanaka S, Nishio S, Marioka T, Fukeri M, Kitemiura K, Ikita K (1989) Radiation-induced osteosarcoma of the sphenoid bone. *Neurosurgery* 25:640-643
3385. Taphetti B, Gatta G, Giunta F, Marini G (1980) Multiple gliomas of the brain: report of three cases. *J Neurosurg Sci* 24:155-161
3386. Tani E, Ametani T (1970) Polygonal cristalline structures in human ependymoma cells. *Acta Neuropathol (Berl)* 15:359-362
3387. Tani E, Higashi N (1972) Intercellular junctions in human ependymomas. *Acta Neuropathol (Berl)* 22:295-304
3388. Tani E, Ikeda K, Yamagata S, Nishiura M, Higashi N (1974) Specialized junctional complexes in human meningioma. *Acta Neuropathol (Berl)* 28:305-315
3389. Tannock IF (1970) Population kinetics of carcinoma cells, capillary endothelial cells and fibroblasts in a transplanted mouse mammary tumor. *Cancer Res* 30:2470-2476
3390. Taphoorn MJB, de Vries-Knoppert WAEJ, Ponssen H, Wolbers JG (1989) Malignant optic glioma in adults. *J Neurosurg* 70:277-279
3391. Taphoorn MJB, Schiphorst AK, Snoek FJ, Lindeboom J, Wolbers JG, Karim ABMF, Huijgens PC, Heimans JJ (1994) Cognitive functions and quality of life in patients with low-grade gliomas: the impact of radiotherapy. *Ann Neurol* 36:48-54
3392. Tapscott SJ, Bennett GS, Toyama Y, Kleinbart F, Holtzen H (1981) Intermediate filament proteins in the developing chick spinal cord. *Develop Biol* 86:40-54
3393. Taptas JN (1961) Intracranial meningioma in a four month old infant simulating subdural hematoma. *J Neurosurg* 18:120-121
3394. Taratuto AL, Molina H, Monges J (1983) Choroid plexus tumors in infancy and childhood. Focal ependymal differentiation. An immunoperoxidase study. *Acta Neuropathol (Berl)* 59:304-308
3395. Taratuto AL, Monges J, Lylyk P, Leiguardes R (1984) Superficial cerebral astrocytoma attached to dura. Report of six cases in infants. *Cancer* 54:2505-2512

3396. Taratuto AL, Pomata H, Sevlever G, Gallo G, Monges J (1995) Dysembryoplastic neuroepithelial tumor: morphological, immunocytochemical, and Deoxyribonucleic acid analyses in a pediatric series. *Neurosurgery* 3:474–481
3397. Tarlov JM (1940) Origin of perineural fibroblastoma. *Amer J Path* 16:33–39
3398. Tascos NA, Parr J, Gonatas NK (1982) Immunocytochemical study of the glial fibrillary acidic protein in human neoplasms of the central nervous system. *Hum Pathol* 13:454–458
3399. Tashiro T, Yoshida J, Mizuno M, Sugita K (1993) Reinforced cytotoxicity of lymphokine-activated killer cells toward glioma cells by transfection with the tumor necrosis factor- $\alpha$  gene. *J Neurosurg* 78:252–256
3400. Tavassoli FA (1986) Melanotic paraganglioma of the uterus. *Cancer* 58:942–948
3401. Taveras JM, Wood EH (1969) Diagnostic neuroradiology. Williams and Wilkins, Baltimore
3402. Tavolato B, Runo F (1974) Multiple sclerosis in the Padova province (Italy). An epidemiological survey. *Acta Neurol Scand* 50:76–90
3403. Taxy JB (1983) Paraganglioma of the cauda equina. Report of a rare tumor. *Cancer* 51:1904–1006
3404. Taylor CR, Russell R, Lukes RJ, Davis RL (1978) An immunohistochemical study of immunoglobulin content of primary central nervous system lymphomas. *Cancer* 41:2197–2205
3405. Teilum G (1965) Classification of endodermal sinus tumors (mesoblastoma vitellinum) and so-called “embryonal carcinoma” of the ovary. *Acta Pathol Microbiol Scand* 64:407–429
3406. Teltscharow L, Zülch KJ (1948) Das Astrocytom des Grosshirns vom pathologisch-anatomischen Standpunkt aus. *Arch Psych Z Neur* 179:691–720
3407. Temple S (1989) Division and differentiation of isolated CNS blast cells in microculture. *Nature* 340:471–473
3408. Tenan M, Colombo BM, Cajola L, Pollo B, Broggi G, Finocchiaro G (1993) Low frequency of NF1 gene mutations in malignant gliomas. *Eur J Cancer* 29:1217–1218
3409. Tenan M, Colombo BM, Pollo B, Cajola L, Broggi G, Finocchiaro G (1994) p53 mutations and microsatellite analysis of heterozygosity in malignant gliomas. *Cancer Genet Cytogenet* 74:139–143
3410. Tenny RT, Laws ER Jr, Younge BR, Rush JA (1982) The neurosurgical management of optic glioma: results in 104 patients. *J Neurosurg* 57:452–458
3411. Tennyson VM, Pappas GD (1961) Electron microscopic studies of the developing telencephalic choroid plexus in normal and hydrocephalic rabbits. In: Fields WS, Desmond MM (eds) *Disorders of the developing nervous system*. Thomas, Springfield
3412. Tennyson VM, Pappas GD (1962) An electron microscope study of ependymal cells of the fetal, early postnatal and adult rabbit. *Z Zellforsch* 56:595–618
3413. Tennyson VM, Pappas GD (1971) Ependyma. In: Minckler J (ed) *Pathology of the nervous system*, vol I. McGraw-Hill, New York, pp 518–530
3414. Terenghi G, Polak JM, Ballesta J, Cocchia D, Michetti F, Dahl D, Marangos PJ, Garner A (1984) Immunocytochemistry of neuronal and glial markers in retinoblastoma. *Virchows Arch [A] Path Anat His* 404:61–74
3415. Thames HD, Peters LJ, Winthers HR, (1983) Accelerated fractionation vs hyperfractionation: rationale for several treatments per day. *Int J Radiat Oncol Biol Phys* 9:127–138
3416. Theaker JM, Gatter KC, Esiri MM, Fleming KA (1986) Epithelial membrane antigen and cytokeratin expression by meningiomas: an immunohistological study. *J Clin Pathol* 39:435–440
3417. Theodore WH, Gendelman S (1981) Meningeal carcinomatosis. *Arch Neurol* 38:696–700
3418. Theuring F, Gotz W, Balling R, Korf H-W, Schultze F, Herken R, Gruss P (1990) Tumorigenesis and eye abnormalities in transgenic mice expressing MSV-SV40 large T-antigen. *Oncogene* 5:225–232
3419. Thibodeau L, Ariza A, Piepmeier JM (1988) Primary leptomeningeal sarcomatosis. *J Neurosurg* 68:802–805
3420. Thiel G, Losonawa T, Kintzel D, Nish G, Martin H, Vorpahl K, Witkowski R (1992) Karyotypes in 90 human gliomas. *Cancer Genet Cytogenet* 58:109–120
3421. Thierry A, Archimbaud JP, Perrin P, Mansuy L (1968) Aspects neurologiques et urologiques particuliers des tumeurs développées sur spina bifida occulta chez l'adulte et le grand enfant. A propos de 2 cas de lipomes lombo-sacrés opérés. *Neurochirurgie (Paris)* 14:809–816

3422. Thomas DGT, Darling JL, Paul EA, (1985) Assay of anticancer drugs in tissue culture: relationship of relapse free interval (RFI) and in vitro chemosensitivity in patients with malignant cerebral glioma. *Br J Cancer* 51:525-532
3423. Thomas GA, Raffel C (1994) Loss of heterozygosity on 6q, 16q and 17p in human central nervous system primitive neuroectodermal tumors. *Cancer Res* 51:639-643
3424. Thomas HG, Dolman CL, Berry K (1981) Malignant meningioma: clinical and pathological features. *J Neurosurg* 55:929-934
3425. Thomas TL, Decoufle P (1979) Mortality among workers employed in the pharmaceutical industry: a preliminary investigation. *J Occup Med* 21:619-623
3426. Thomas TL, Waxweiler RJ (1986) Brain tumors and occupational risk factors: a review. *Scand J Work Environ Health* 12:1-15
3427. Thomas TL, Stolley PD, Stemhagen A, Fontham ETH, Bleecker ML, Stewart PA, Hoover RN (1987) Brain tumor mortality risk among men with electrical and electronics jobs: a case-control study. *J Natl Cancer Inst* 79:233-237
3428. Thomas TL, Waxweiler RJ, Crandell MS (1982) Brain cancer among Okaw members in three Texas oil refineries. *Ann NY Acad Sci* 381:120-129
3429. Thompson JR, Harwood-Nash DC, Fitz CR (1973) The neuroradiology of childhood choroid plexus neoplasm. *Am J Roentgenol* 117:116-133
3430. Thompson SA (1982) Localization of immunoreactive prolactin in ependyma and circumventricular organs of rat brain. *Cell Tissue Res* 225:79-83
3431. Thoms OJ, Shaw DT, Trowbridge WV (1960) Glomus jugulare tumor. Report of a case with surgical removal. *J Neurosurg* 17:500-504
3432. Thorgerisson UP, Lindsay CK, Cottam DW, Gomez DE (1994) Tumor invasion, proteolysis, and angiogenesis. *J Neurooncol* 18:89-103
3433. Thorne RN, Pearson ADJ, Nicoll JAR, Coakham HB, Oakbill A, Mott MG, Foreman NK (1994) Decline in incidence of medulloblastoma in children. *Cancer* 74:3240-3244
3434. Thornton C, Brennan F, Hawkins SA, Allen IV (1988) Primary malignant melanoma of the meninges. *Clin Neuropathol* 5:244-248
3435. Tibbs PA, Mortara RH (1980) Primary glioblastoma multiforme of the cerebellum. A case report. *Acta Neurochir (Wien)* 52:13-18
3436. Tiberin P, Maor E, Zaizov R, Cohen IJ, Nirsch M, Yosefovich T, Ronen J, Goldstein J (1984) Brain sarcoma of meningeal origin after cranial irradiation in childhood acute lymphocytic leukemia. *J Neurosurg* 61:772-776
3437. Tjissen CC (1986) Genetic factors and family studies in medulloblastoma. In: Zelter PM, Pochedly C (eds) *Medulloblastoma in children. New concepts in tumor biology, diagnosis and treatment*. Praeger, New York, pp 61-73
3438. Till K (1982) Craniopharyngioma. *Childs Brain* 9:179-187
3439. Tilzer LL, Plapp FV, Evans JP, Stone D, Alward K (1982) Steroid receptor proteins in human meningiomas. *Cancer* 49:633-636
3440. Timperley WR (1971) Lactate dehydrogenase isoenzymes in tumours of the nervous system. *Acta Neuropathol (Berl)* 19:20-24
3441. Toglia JU, Netsky MG, Alexander E (1965) Epithelial (epidermoid) tumors of the cranium. Their common nature and pathogenesis. *J Neurosurg* 23:384-393
3442. Tohyama T, Lee VM-Y, Rorke LB, Marvin M, McKay RDG, Trojanowski JQ (1992) Nestin expression in embryonic human neuroepithelium and in human neuroepithelial tumor cells. *Lab Invest* 66:301-313
3443. Tolle SW, Dyson RD, Newburg RW, Cardenas JM (1976) Pyruvate kinase isoenzymes in neurons, glia, neuroblastoma, and glioblastoma. *J Neurochem* 27:1355-1360
3444. Tomita T, McLone DG (1986) Medulloblastoma in childhood: results of radical resection and low-dose neuraxis radiation therapy. *J Neurosurg* 64:238
3445. Tomita T, Naidich TP (1987) Successful resection of choroid plexus papillomas diagnosed at birth: report of 2 cases. *Neurosurgery* 20:774-779
3446. Tomita T, McLone DG, Naidich TP (1984) Brain stem gliomas in childhood. Rational approach and treatment. *J Neurooncol* 2:117-122
3447. Tomita T, David G, McLone DG, Masaharu Y (1988) Cerebral primitive neuroectodermal tumors in childhood. *J Neurooncol* 6:233-243

3448. Tomita T, Yasne M, Engelhard HH, McLone DG, Gonzales-Crussi F, Bauer KD (1988) Flow cytometry DNA analysis of medulloblastoma. *Cancer* 61:744–749
3449. Tomlinson FH, Kurtin PJ, Suman VJ, Scheithauer BW, O'Fallon JR, Kelly PJ, Jack CR, O'Neill BP (1995) Primary intracerebral malignant lymphoma: a clinico-pathological study of 89 patients. *J Neurosurg* 82:558–566
3450. Tonelli L (1950) I tumori della notocorda. Clinica delle diverse localizzazioni, studio e proposta di un nuovo schema ordinativo. *Arch De Vecchi Anat Pathol* 15:471–607
3451. Tönnis W, Nittner K (1968) Diagnostische Probleme bei Sanduhrgeschwülsten des Spinalkanals. *Dtsch Zbl Nervenheilk* 194:219–231
3452. Torres LE, Grant N, Harding BN, Scaravilli F (1985) Intracerebral neuroblastoma: report of a case with neuronal maturation and long survival. *Acta Neuropathol (Berl)* 68:110–114
3453. Townsend JJ, Seaman JP (1986) Central neurocytoma – a rare benign intraventricular tumor. *Acta Neuropathol (Berl)* 71:167–170
3454. Traflet RF, Barbaria AR, Barolat G, Doan HT, Gonzales C, Mishkin MM (1989) Intracranial chondroma in a patient with Ollier's disease. *J Neurosurg* 70:274–276
3455. Treip CS (1957) A congenital medulloepithelioma of the midbrain. *J Pathol Bacteriol* 74:357–363
3456. Trent J, Meltzer P, Rosemblum M, Harsh G, Kinnzler K, Mashal R, Feinberg A, Vogelstein B (1986) Evidence for rearrangement, amplification, and expression of c-myc in a human glioblastoma. *Proc Natl Acad Sci USA* 83:470–473
3457. Treynor JE, Casey HW (1971) Five-year follow-up of primates exposed to 55 MeV protons. *Radiat Res* 47:143–148
3458. Trimble WS, Schneller RH (1988) Molecular biology of synaptic vesicle-associated proteins. *TINS* 11:241–242
3459. Trofatter JA, MacCollin MM, Rutter JL, Murrel JR, Duyao MP, Parry DM, Eldridge R, Kley N, Menon AG, Pulaski K, Haase UH, Ambrose CM, Monroe D, Bove C, Haines JL, Martuza RL, McDonald ME, Seizinger BR, Short MP, Bukler AJ, Gusella JF (1993) A novel moesin-, ezrin-, radixin-like gene is a candidate for the neurofibromatosis 2 tumor suppressor. *Cell* 72:791–800
3460. Trojan J, Blossey BK, Johnson TR, Rudin SD, Tykocinski M, Ilan J (1992) Loss of tumorigenicity of rat glioblastoma directed by episome-based antisense cDNA transcription of insulin-like growth factor I. *Proc Natl Acad Sci USA* 89:4874–4878
3461. Trojan J, Johnson TR, Rudin SD, Ilan J, Tykocinski ML (1993) Treatment and prevention of rat glioblastoma by immunogenic C6 cells expressing antisense insulin-like growth factor I RNA. *Science* 259:94–97
3462. Trojanowski JQ (1990) Primitive neuroectodermal tumors recapitulate stages in the normal differentiation of neural cells of the developing nervous system. Symposium on Brain Tumor Pathology, 9–10 September, Biwako, Japan, p 26
3463. Trojanowski JQ, Lee V (1983) Anti-neurofilament monoclonal antibodies reagents for the evaluation of human neoplasms. *Acta Neuropathol (Berl)* 59:155–158
3464. Trojanowski JQ, Lee VMY, Schlapfer WW (1984) An immunohistochemical study of human central and peripheral nervous system tumors, using monoclonal antibodies against neurofilaments and glia filaments. *Hum Pathol* 15:248–257
3465. Trojanowski JQ, Friedman HS, Burger PC, Bigner DD (1987) A rapidly dividing human medulloblastoma cell line (D283 med) express all three neurofilament subunits. *Am J Pathol* 126:358–363
3466. Troost D, Tulleken CAF (1984) Malignant glioma after bombshell injury. *Clin Neuropathol* 3:139–142
3467. Ts'o MOM, Fine BS, Zimmerman LE (1969) The Flexner-Wintersteiner rosettes in retinoblastoma. *Arch Pathol* 88:664–671
3468. Ts'o MOM, Zimmerman LE, Fine BS (1970) The nature of retinoblastoma. I. Photoreceptor differentiation. A clinical and histopathologic study. *Am J Ophthalmol* 69:339–349
3469. Tsang RW, Laperriere NJ, Simpson WJ, Brierley J, Panzarella T, Smyth AS (1993) Glioma arising after radiation therapy for pituitary adenoma. A report of four patients and estimation of risk. *Cancer* 72:2227–2233

3470. Tsuda T, Obara M, Hirano H, Gotoh S, Kubomura S, Higashi K, Kuroiwa A, Nakagawara A, Nagahara N, Shimizu K (1987) Analysis of N-myc amplification in relation to disease stage and histologic types in human neuroblastomas. *Cancer* 60:820-826
3471. Tsukada J, Fouad A, Pickren JW, Lane WW (1983) Central nervous system metastasis from breast carcinoma. Autopsy study. *Cancer* 52:2349-2355
3472. Tsuruda JS, Kortman KE, Bradley WG, Wheeler DC, Van Dalsem W, Bradley TP (1987) Radiation effects on cerebral white matter: MR evaluation. *AJNR* 8:431-437
3473. Tukanowicz SA, Grant FC (1958) The meningiomas of the lateral ventricles of the brain. *J Neuropathol Exp Neurol* 17:367-381
3474. Turnbull IM, Tom MI (1963) Pigmented meningioma. *J Neurosurg* 20:76-80
3475. Twist EC, Ruttledge MH, Rousseau M, Sanson M, Papi L, Merel P, Delattre O, Thomas G, Rouleau GA (1994) The neurofibromatosis type 2 gene is inactivated in schwannomas. *Hum Molec Genet* 3:147-151
3476. Tyler JL, Diksik M, Villemure J-G, Evans AC, Meyer E, Yamamoto YL, Feindel W (1987) Metabolic and hemodynamic evaluation of gliomas using positron emission tomography. *J Nucl Med* 28:1123-1123
3477. Tym R (1969) Distribution of cell doubling times in human cerebral tumors. *Surg Forum* 20:445-452
3478. Tytus JS, Pennybacker J (1956) Pearly tumours in relation to the central nervous system. *J Neurol Neurosurg Psychiatry* 19:241-259
3479. Tzaan WC, Ho YS, Chang CN, Lin TK, Wong CW (1992) Intraventricular neurocytoma: four cases report. *J Neurooncol* 13:239-246
3480. Tzonos T, Brunngraber CV (1963) Ueber ein Medulloblastom mit Riesenzellen. *Zbl Neurochir* 23:282-285
3481. Tzonos T, Pfingst E (1967) Malignes Gangliozytom des Kleinhirns. *Zbl Neurochir* 28:323-327
3482. Ueba T, Takahashi JA, Fukumoto M, Ohta M, Ito N, Oda Y, Kikuchi H, Hatanaka M (1994) Expression of fibroblast growth factor receptor-1 in human glioma and meningioma tissues. *Neurosurgery* 34:221-225
3483. Ueck M, Wake K (1979) The pinealocyte - a paraneuron. *Prog Brain Res* 52:141-147
3484. Ueki K, Rubio M-P, Ramesh V, Correa KM, Rutter JL, von Deimling A, Buckler AJ, Gusella JE, Louis DN (1994) MTS1/CDKN2 gene mutations are rare in primary human astrocytomas with allelic loss of chromosome 9p. *Hum Molec Genet* 3:1841-1845
3485. Uematsu Y, Itakura T, Hayashi S, Komai N (1988) Pineoblastoma with an unusually long survival. *J Neurosurg* 69:287-291
3486. Ulich TR, Mirra JM (1982) Ecchordosis physaliphora vertebralis. *Clin Orthop Relat Res* 163:282-289
3487. Ulrich J (1964) Intracranial epidermoids. A study on their distribution and spread. *J Neurosurg* 21:1051-1058
3488. Upadhyaya M, Shaw DJ, Harper PS (1994) Molecular basis of neurofibromatosis type 1 (NF1): Mutation analysis and polymorphisms in the NF1 gene. *Hum Mutat* 4:83-101
3489. Urbánek P, Wang ZQ, Fetka I, Wagner EF, Busslinger M (1994) Complete block of early B cell differentiation and altered patterning of the posterior midbrain in mice lacking Pax5/BSAP. *Cell* 79:901-912
3490. Ushio Y, Arita N, Hayakawa T, Yamada K, Koh S, Nagatani M, Yoshimine T, Mogami H (1987) Leptomeningeal dissemination of primary brain tumors in children: clinical and experimental studies. In: Kageyama N, Takakura K, Epstein F, Hoffman HJ, Schut L (eds) *Intracranial tumors of infancy and childhood. Basic research, diagnosis and treatment. Progr Exp Tumor Res* 30:194-205
3491. Ushio Y, Arita N, Yoshimine I, Nagatani M, Mogami H (1987) Glioblastoma after radiotherapy for craniopharyngioma: Case report. *Neurosurgery* 21:33-38
3492. Utley JF, Marlowe C, Wandell JW (1976) Distribution of S-35 labelled WR-2721 in normal and malignant tissues of the mouse. *Radiat Res* 68:248-291
3493. Vagner-Capodano AM, Gentet JC, Choux M, Lena G, Garbarelli D, Bernard JL, Rayband C (1989) Chromosomal abnormalities in 16 pediatric brain tumors. *Pediatr Neurosci* 14:150-160
3494. Vailati G, Occhiogrosso M, Troccoli V (1979) Intramedullary thoracic schwannoma. *Surg Neurol* 11:60-62

3495. Valdueza JM, Hagel C, Westphal M, Hansel M, Hermann HD (1991) Primary spinal malignant Schwannoma: clinical, histological and cytogenetic findings. *Neurosurg Rev* 14:283–291
3496. Valentino KL, Jones EC, Kane SA (1983) Expression of GFAP immunoreactivity during development of long fiber tracts in the rat CNS. *Develop Brain Res* 9:317–336
3497. Valk PE, Dillon WP (1991) Radiation injury of the brain. *AJNR* 12:45–62
3498. Vallee B, Malhaire JP, Person H, Colin J (1984) Delayed cerebral pseudo-tumoral radionecrosis following scalp-tumour irradiation. Case report and review of literature. *J Neurol* 231:135–140
3499. Van Alphen HAM, Bellor SM, Stam FC (1976) Paraganglioma of cauda equina. *Clin Neurol Neurosurg* 799:316–322
3500. Van Bogaert L (1948) La mélanose neurocutanée diffuse hérédofamiliale. *Bull Acad Roy Med Belg* 13:397–428
3501. Van den Berge JH, Blaau WG, Breeman NAP, Rahmy A, Wijngaarde R (1992) Intracavitary brachytherapy of cystic craniopharyngiomas. *J Neurosurg* 77:545–550
3502. Van den Pol AN, Cassidy JR (1982) The hypothalamic arcuate nucleus of rat. A quantitative Golgi analysis. *J Comp Neurol* 204:65–98
3503. Van der Hoeve J (1933) Les phacomatoses de Bourneville, de Recklinghausen et de von Hippel-Lindau. *J Belge Neurol Psychiatr* 33:752–762
3504. Van der Kogel AJ (1977) Radiation tolerance of the rat spinal cord: time-dose relationships. *Radiology* 122:505–509
3505. Van der Kogel AJ (1980) Mechanism of late radiation injury in the spinal cord. In: Meyn RE, Withers HR (eds) *Radiation biology in cancer research*. Raven, New York, pp 461–470
3506. Van der Kogel AJ (1986) Radiation-induced damage in the central nervous system: an interpretation of target cell response. *Br J Cancer* 53:207–217
3507. Van der Meulen JD, Houthoff HJ, Ebels EJ (1978) Glial fibrillary acidic protein in human gliomas. *Neuropathol Appl Neurobiol* 4:177–190
3508. Van der Mey AGL, Fruns JHM, Cornelisse CJ, Brons EN, Dulken von H, Terfistra HL, Schmidt PH (1992) Does intervention improve the natural course of glomus tumors? A series of 108 patients seen in 32 year period. *Ann Otol Rhinol Laryngol* 101:635–642
3509. Van der Schueren E, Landuyt W, Ang KK, Van der Kogel AJ (1988) From 2 Gy to 1 Gy per fraction: sparing effect in rat spinal cord? *Int J Radiat Oncol Biol Phys* 14:297–300
3510. Van Dilla MA, Steinmetz LL, David DT, Calvert RN, Gray JW (1974) High-speed cell analysis and sorting with flow system: biological applications and new approaches. *Nucl Sci* 21:714–720
3511. Van Epps RR, Samuelson DR, McCormick WT (1967) Cerebral medulloepithelioma: case report. *J Neurosurg* 27:568–573
3512. Van Gilder JC, Inukai J (1973) Growth characteristics of experimental intracerebellary transplanted oral epithelium. *J Neurosurg* 38:608–615
3513. van Meyel DJ, Ramsay DA, Casson AG, Keeney M, Chambers AF, Cairncross JG (1994) p53 mutation, expression, and DNA ploidy in evolving gliomas: Evidence for two pathways of progression. *J Natl Cancer Inst* 86:1011–1017
3514. van Meyel DJ, Ramsay DA, Chambers AF, Macdonald DR, Cairncross JG (1994) Absence of hereditary mutations in exons 5 through 9 of the p53 gene and exon 24 of the neurofibromin gene in families with glioma. *Ann Neurol* 35:120–122
3515. Van Wagenen WP (1930) Papillomas in the choroid plexus. Report of two cases, one with removal of the tumor at operation, and one with “seeding” of tumor in the ventricular system. *Arch Surg* 20:199–231
3516. VandenBerg SR (1992) Current diagnostic concepts of astrocytic tumors. *J Neuropathol Exp Neurol* 51:644–657
3517. VandenBerg SR (1993) Desmoplastic infantile ganglioglioma and desmoplastic cerebral astrocytoma of infancy. *Brain Pathol* 3:275–281
3518. VandenBerg SR, May EE, Rubinstein LJ, Herman MM, Perentes E, Vinore SA, Collins VP, Park TS (1987) Desmoplastic supratentorial neuroepithelial tumors of infancy with divergent differentiation potential (‘desmoplastic infantile gangliogliomas’). Report on 11 cases of a distinctive embryonal tumor with favorable prognosis. *J Neurosurg* 66:58–71
3519. Vaquero J, Manrique M, Oya S, Cabezuto JM, Bravo G (1980) Calcified teleangiectatic hamartomas of the brain. *Surg Neurol* 13:453–457

3520. Vaquero J, Leunda G, Cabezudo JM, Salazar AR, De Miguel J (1981) Granular pituicytomas of the pituitary stalk. *Acta Neurochir (Wien)* 59:209–215
3521. Vaquero J, Martinez R, Rossi E, Lopez R, Rothballer AB, Puljic S, Poon TP (1984) Primary cerebral lymphoma: the “ghost tumor”. Case report. *J Neurosurg* 60:174–176
3522. Vaquero J, Martinez R, Vegazo I, Pontòn P (1989) Subependymoma of the cervical spinal cord. *Neurosurgery* 24:625–627
3523. Varakis JN, Zurhein GM (1976) Experimental pineocytoma of the Syrian Hamster induced by a human papovavirus (JC). *Acta Neuropathol (Berl)* 35:243–264
3524. Varma RR, Crumrine PK, Bergman I, Latchaw RE, Price RA, Vries J, Painter MJ (1983) Childhood oligodendrogliomas presenting with seizures and low density lesions on computed tomography. *Neurology* 33:806–808
3525. Varon SS, Somjen GG (1979) Neuron-glia interaction. *Neurosci Res Program Bull* 17:42–65
3526. Vasquez Lopez E (1945) Glioma in a rat fed with 2-acetyl-aminofluorene. *Nature* 156:296–297
3527. Vassilouthis J, Richardson AE (1980) Subfrontal schwannoma. *Acta Neurochir (Wien)* 53:259–266
3528. Vaughn JE (1969) An electronmicroscopic analysis of gliogenesis in rat optic nerves. *Z Zellforsch* 94:293–324
3529. Vaughn JE, Hinds PL, Skoff RP (1970) Electron microscopy studies of wallerian degeneration in rat optic nerves. I. The multipotential glia. *J Comp Neurol* 140:175–206
3530. Vecht CJ (1993) Effect of age on treatment decisions in low-grade glioma. *J Neurol Neurosurg Psychiatry* 56:1259–1264
3531. Vecht CJ, Avezaat CJJ, Van Putten WLJ, Eijkmboom WHM, Stefanko SZ (1990) The influence of the extent of surgery on the neurological function and survival in malignant glioma. A retrospective analysis in 243 patients. *J Neurol Neurosurg Psychiatr* 53:466–471
3532. Vecht CJ, Haaxma-Reiche H, Noordijk EM, Patberg GW, Voormolen JHC, Hoekstra FH, Tans JTJ, Nambooi N, Metsaars JAL, Wattendorff AR, Brand R, Hermans J (1993) Treatment of single brain metastasis: radiotherapy alone or combined with neurosurgery? *Ann Neurol* 33:583–590
3533. Velasco ME, Dahl D, Roessmann U, Gambetti P (1980) Immunohistochemical localization of glial fibrillary acidic protein in human glial neoplasms. *Cancer* 45:484–494
3534. Velasco ME, Ghobrial MW, Ross ER (1985) Neuron-specific enolase and neurofilament protein as markers of differentiation in medulloblastoma. *Surg Neurol* 23:177–182
3535. Velema JP, Walker AD (1987) The age curve of nervous system tumor incidence in adults: common shape but changing levels by sex, race and geographical location. *Int J Epidemiol* 16:177–183
3536. Venitt S, Searle CE (1976) Mutagenicity and possible carcinogenicity of hair colourants and constituents. *IARC Sci Publ* 13:263–272
3537. Venkataramana NK, Kolluri VRS, Kumar DVR, Rao TV, Das BS (1989) Paraganglioma of the orbit with extension to the middle cranial fossa: case report. *Neurosurgery* 24:762–764
3538. Venter DJ, Bevan KL, Ludwig RL, Riley TE, Jat PS, Thomas DJ, Noble MD (1991) Retinoblastoma gene deletions in human glioblastomas. *Oncogene* 6:445–448
3539. Verga P (1929) Lipomi ed osteolipomi della pia madre. *Tumori* 15:321–333
3540. Verkijk A, Bots GT (1980) An intrasellar cyst with both Rathke’s cleft and epidermoid characteristics. *Acta Neurochir (Wien)* 51:203–207
3541. Vertosick FT, Selker RG, Arena VC (1991) Survival of patients with well-differentiated astrocytomas diagnosed in the era of computed tomography. *Neurosurgery* 28:496–501
3542. Verzat C, Delisle M-B, Courriere P, Hollande E (1990). Influence of host sex on the growth of a human glioblastoma line in athymic mice. *Neuropathol Appl Neurobiol* 16:141–151
3543. Viale GL (1968) Tumori rari della regione sellare. *Riv Neurol* 38:210–236
3544. Viale GL (1969) Biochemical patterns in brain tumours. II. Enzymes of the tricarboxylic acid cycle. *Acta Neurochir (Wien)* 20:273–279
3545. Viererger P, Gerhard L, Nahser HC (1987) Familial glioma: occurrence in the ‘familial cancer syndrome’ and systemic malformations. *J Neurol* 234:220–232
3546. Vilches J, Lopez A, Martinez MC, Gomez J, Barbera J (1981) Scanning and transmission electron microscopy study of a craniopharyngioma: X-ray microanalytical study of the intratumoral mineralized deposits. *Ultrastruct Pathol* 2:343–356



3547. Villani R, Gaini SM, Tomei G (1975) Follow-up study of brain stem tumors in children. *Childs Brain* 1:126–135
3548. Vinken PJ, Slooff ACJ (1965) A case of carcinoma of the choroid plexus in a child. *Zbl Neurochir* 26:313–316
3549. Vinorez SA (1991) Demonstration of glial fibrillary acidic (GFA) protein by electron immunocytochemistry in the granular cells of a choristoma of the neurohypophysis. *Histochemistry* 96:265–269
3550. Vinorez SA, Koestner A (1982) Reduction of ethylnitrosourea-induced neoplastic proliferation in rat trigeminal nerves by nerve growth factor. *Cancer Res* 42:1038–1040
3551. Vinorez SA, Rubinstein LJ (1985) Simultaneous expression of glial fibrillary acidic (GFA) protein and neuron-specific enolase (NSE) by the same reactive or neoplastic astrocyte. *Neuropathol Appl Neurobiol* 11:349–359
3552. Vinorez SA, Herman MM, Katsetos CD, May EE, Frankfurter A (1994) Neuron-associated class III  $\beta$ -tubulin, tau and MAP2 in the D-283 Med cell line and in primary explants of human medulloblastoma. *Histochem J* 26:678–685
3553. Vinters HV, Gatti RA, Rakic P (1985) Sequence of cellular events in cerebellar ontogeny relevant to expression of neuronal abnormalities in ataxia-telangiectasia. In: Gatti RA, Swift M (eds) *Ataxia-telangiectasia*. Liss, New York, pp 233–245
3554. Virchow R (1857) Untersuchungen über die Entwicklung des Schädelgrundes im gesunden und krankhaften Zustand und über den Einfluss derselben auf Schädelform, Gesichtsbildung und Gehirnbau. Reimer, Berlin
3555. Virchow R (1863) Die krankhaften Geschwülste. Hirschwald, Berlin
3556. Virchow R (1900) Das Psammom. *Virch Arch (A)* 160:32
3557. Viskochil D, Buchberg A, Xu G, Cawthon RW, Stevens J, Wolff RK, Culver M, Carey JC, Copeland NG, Jenkins NA, White R, O'Connell P (1990) Deletions and a traslocation interrupt a cloned gene at the neurofibromatosis type 1 locus. *Cell* 62:187–192
3558. Vlodawsky I, Sullivan R, Fridman R, Sane J, Folkman J, Klagsbrun R (1986) Heparin binding endothelial cell growth factor produced by endothelial cells and sequestered by the subendothelial extracellular matrix. *J Cell Biol* 103, (No 5), part 2, 98a
3559. Vogel FS, Stevenson LD (1950) Meningothelial meningioma of the fourth ventricle. *J Neuropathol Exp Neurol* 9:443–448
3560. Vogelstein B, Kinzler KW (1992) p53 funtion and dysfunction. *Cell* 70:523–526
3561. Voigt K, Yasargil MG (1976) Cerebral cavernous haemangiomas or cavernomas: incidence, pathology, localization, diagnosis, clinical features and treatment. Review of the literature and report of an unusual case. *Acta Neurochir (Wien)* 19:59–63
3562. Volkow N, Goldman SS, Flamm ES, Cravioto H, Wolf AP, Brodie JD (1983) Labeled putrescine as a probe in brain tumors. *Science* 221:673–675
3563. von Deimling A, Janzen R, Kleihues P, Wiestler OD (1990) Patterns of differentiation in central neurocytoma. An immunohistochemical study of eleven biopsies. *Acta Neuropathol (Berl)* 79:473–479
3564. von Deimling A, Louis DN, von Ammon K, Petersen I, Hoell T, Chung RY, Martuza RL, Schoenfeld DA, Yasargil MG, Wiestler OD, Seizinger BR (1992) Association of epidermal growth factor receptor gene amplification with loss of chromosome 10 in human glioblastoma multiforme. *J Neurosurg* 77:295–301
3565. von Deimling A, Eibl RH, Ohgaki H, Louis DM, von Ammon K, Petersen I, Kleihues P, Chung RY, Wiestler OD, Seizinger BR (1992) p53 mutations are associated with 17p allelic loss in grade II and grade III astrocytoma. *Cancer Res* 52:2987–2990
3566. von Deimling A, Louis DN, von Ammon K, Petersen I, Wiestler OD, Seizinger BR (1992) Evidence for a tumor suppressor gene on chromosome 19q associated with human astrocytomas, oligodendrogliomas, and mixed gliomas. *Cancer Res* 52:4277–4279
3567. von Deimling A, Louis DN, Menon AG, von Ammon K, Petersen I, Ellison D, Wiestler OD, Seizinger BR (1993) Deletions on the long arm of chromosome 17 in pilocytic astrocytoma. *Acta Neuropathol (Berl)* 86:81–85
3568. von Deimling A, von Ammon K, Schoenfeld D, Wiestler OD, Seizinger BR, Louis DN (1993) Subsets of glioblastoma multiforme defined by molecular genetic analysis. *Brain Pathol* 3:19–26

3569. von Deimling A, Bender B, Jahnke R, Waha A, Kraus J, Albrecht S, Wellenreuther R, Fasbender F, Nagel J, Menon A G, Louis DN, Lenartz D, Schramm J, Wiestler OD (1994) Loci associated with malignant progression in astrocytomas: a candidate on chromosome 19q. *Cancer Res* 54:1397–1401
3570. von Deimling A, Nagel J, Bender B, Lenartz D, Schramm J, Louis DN, Wiestler OD (1994) Deletion mapping of chromosome 19 in human gliomas. *Int J Cancer* 57:676–680
3571. Von Deimling A, Krone W, Menon AG (1995) Neurofibromatosis Type 1: Pathology, clinical features and molecular genetics. *Brain Pathol* 5:153–162
3572. Von der Stein B, Schröder R (1991) Three dimensional reconstruction of some vessel types in meningeal hemangiopericytoma. *Clin Neuropathol* 10:279–284
3573. Von Hanwehr RI, Hofman FM, Taylor CR, Apuzzo MLJ (1984) Mononuclear lymphoid populations infiltrating the microenvironment of primary CNS tumors. *J Neurosurg* 60:1138–1147
3574. Von Monakow C (1924) Gliom und Schädeltrauma. *Schweiz Arch Neur* 14:289–300
3575. Von Santha K (1936) Diffuse Lemnoblakose des Zentralnervensystems. *Z Neur* 154:763–777
3576. von Waechter R, Jaensch C (1972) Generation times of matrix cells during embryonic development. An autoradiographic study in rats. *Brain Res* 46:235–250
3577. Vonderahe AR, Niemi WT (1944) Intracranial lipoma. A report of four cases. *J Neuropathol Exp Neurol* 3:344–355
3578. Vraa-Jensen J, Herman MNM, Rubinstein LJ, Bignami A (1976) In vitro characteristics of a fourth ventricle ependymoma maintained in organ culture systems. Light and electron microscopic observations. *Neuropathol Appl Neurobiol* 2:349–364
3579. Vrignaud P, Londos-Gagliardi D, Robert J (1986) Cellular pharmacology of doxorubicin in sensitive and resistant rat glioblastoma cells in culture. *Oncology* 43:60–66
3581. Waelti E, Markwalder TM (1989) Endocrine manipulation of meningiomas with medroxyprogesterone acetate: effect of MPA on growth of primary meningioma cells in monolayer tissue culture. *Surg Neurol* 31:96–100
3582. Waga S, Handa H, Yamashita J (1979) Intracranial germinoma: treatment and results. *Surg Neurol* 11:167–172
3583. Waga S, Morikawa A, Sakakura M (1979) Craniopharyngioma with midbrain involvement. *Arch Neurol* 36:319–320
3584. Waggner JD (1966) Ultrastructure of benign peripheral nerve sheath tumors. *Cancer* 19:699–709
3585. Waggner JD, Beggs JL (1976) Vasculature of neural neoplasms. *Adv Neurobiol* 15:27–42
3586. Wagman AD, Weiss EK, Riggs HE (1960) Hyperplasia of the skull associated with intraosseous meningioma in the absence of gross tumor. Report of three cases. *J Neuropathol Exp Neurol* 19:111–115
3587. Wakai S, Arai T, Nagai M (1984) Congenital brain tumors. *Surg Neurol* 21:597–609
3588. Wakai S, Segawa H, Kitahara S, Asano T, Sano K, Ogihara R, Tomita S (1984) Teratoma in the pineal region in two brothers. Case reports. *J Neurosurgery* 53:239–243
3589. Wakai S, Neda Y, Inoh S, Nagai M (1985) Angiographically occult angiomas: a report of thirteen cases with analysis of the cases documented in the literature. *Neurosurgery* 17:549–556
3590. Wald SL, Liwnicz BH, Truman TA, Khodadad G (1982) Familial primary nervous system neoplasms in three generations. *Neurosurgery* 11:12–15
3591. Waldmann TA, Levin EH, Baldwin M (1961) The association of polycythemia with a cerebellar hemangioblastoma: the production of an erythropoiesis stimulating factor by the tumor. *Am J Med* 31:318–324
3592. Walker AE, Johnson HC, Browne KM (1952) Hemangiomas of the fourth ventricle. *J Neuropathol Exp Neurol* 11:103–115
3593. Walker AE, Robins M, Weinfeld FD (1985) Epidemiology of brain tumors: the national survey of intracranial neoplasms. *Neurology* 35:219–226
3594. Walker DG, Duan W, Popovic EA, Kaye AH, Tomlinson FH, Lavin M (1995) Homozygous deletions of the multiple tumor suppressor gene 1 in the progression of human astrocytomas. *Cancer Res* 55:20–23
3595. Walker MD, Alexander E Jr, Hunt WE, MacCarthy CS, Mahaley MS, Mealey J, Norrell HA, Owens G, Ransohoff J, Wilson CB, Gehan EA, Strike TA (1978) Evaluation of BCNU and/or

- radiotherapy in the treatment of anaplastic gliomas: a cooperative clinical trial. *J Neurosurg* 49:333–343
3596. Wallace MR, Marchuk DA, Andersen LB, Lechter R, Oden H, Saulino A, Fountain JW, Brereton A, Nicholson J, Mitchell AL, Brownstein BH, Collins FS (1990) Type 1 neurofibromatosis gene: identification of a large transcript disrupted in three patients. *Science* 249:182–186
  3597. Wallen CA, Michaelson SM, Wheeler KT (1980) Evidence for an unconventional radiosensitivity of rat 9L subcutaneous tumors. *Radiat Res* 84:529–541
  3598. Wallner KE, Gonzales M, Sheline GE (1988) Treatment of oligodendrogliomas with or without postoperative radiation. *J Neurosurg* 68:684–688
  3599. Walsh J, Gye R, Connelley TJ (1969) Meningioma: a late complication of head injury. *Med J Aust* 1:906–908
  3600. Walsh JW, Zimmer SG, Oeltgen J (1987) Invasiveness in primary intracranial tumors: Part 2. Studies with scanning electron microscopy of cell surface alterations associated with invasiveness. *Neurosurgery* 21:361–370
  3601. Walter GF, Brucher JM (1979) Ultrastructural study of medulloblastoma. *Acta Neuropathol (Berl)* 48:211–214
  3602. Walter GF, Kleintert R (1987) Dysontogenetic brain tumors. Proposal for an improved classification. *Neuropathol Appl Neurobiol* 13:273–287
  3603. Walter KA, Cahan MA, Gur A, Tyler B, Hilton J, Colvin OM, Burger PC, Domb A, Brem H (1994) Interstitial taxol delivered from a biodegradable polymer implant against experimental malignant glioma. *Cancer Res* 54:2207–2212
  3604. Walter W, Schettler G, Müller W (1969) Zur Klinik und Operabilität der rasch wachsenden Grosshirngliome. *Dtsch Z Nervenheilk* 196:1–19
  3605. Waltz TA, Brownell B (1966) Sarcoma: a possible late result of effective radiation therapy for pituitary adenoma. *J Neurosurg* 24:901–907
  3606. Wanebo JE, Malik JM, VandenBerg SR, Wanebo HJ, Driesen N, Persing JA (1993) Malignant peripheral nerve sheath tumors. A clinicopathologic study of 28 cases. *Cancer* 71:1247–1253
  3607. Wang A-M, Skias DD, Rumbaugh CL, Schoene WC, Zamani A (1983) Central nervous system changes after radiation therapy and/or chemotherapy: correlation of CT and autopsy findings. *AJNR* 4:466–471
  3608. Wang J-L, Nistér M, Hermansson M, Westermark B, Pontén J (1990) Expression of PDGF b-receptors in human meningioma cells. *Cancer Res* 46:772–778
  3609. Wara WM, Sheline GE, Newman H, Townsend JJ, Boldrey EB (1975) Radiation therapy of meningiomas. *AJR* 123:453–458
  3610. Wara WM, Begg A, Phillips TL, Rosenblum ML, Vasquez D, Wilson CB (1977) Growth and treatment of human brain tumors in nude mice – preliminary communication. In: Houchens DP, Ovejera AA (eds) *The use of athymic (nude) mice in cancer research*. Fischer, New York, pp 251–256
  3611. Wara WM, Jenkin RDT, Evans A, Ertel I, Hittle R, Ortega J, Wilson CB, Hammond D (1979) Tumors of the pineal and suprasellar region: Childrens Cancer Study Group. *Cancer* 43:698–701
  3612. Warburg O (1930) *The metabolism of tumors*. Arnold, London, pp 75–327
  3613. Warne PC, Blasberg RG, Groothuis DR (1987) The effect of hyperosmotic blood-brain barrier disruption on blood-to-tissue transport in ENU-induced gliomas. *Ann Neurol* 22:300–305
  3614. Washiyama K, Sekiguchi K, Tanaka R, Yamazaki K, Kumanishi T, Oyake Y (1987) Immunohistochemical study on AFP, HCG and PLAP in primary intracranial germ cell tumors. *Progr Exp Tumor Res* 30:296–306
  3615. Wasson JC, Saylor RL, Zelter P, Friedman HS, Bigner SH, Burger PC, Bigner DD, Look AT, Douglass EC, Brodeur GM (1990) Oncogene amplification in pediatric brain tumors. *Cancer Res* 50:2087–2090
  3616. Watanabe K, Nagai M, Wakai S, Arai T, Kawashim A (1990) Loss of constitutional heterozygosity in chromosome 10 in human glioblastoma. *Acta Neuropathol (Berl)* 80:251–254
  - 3616a. Watanabe K, Tachibana O, Sato K, Yonekawa Y, Kleihues P, Ohgaki H (1996) Overexpression of the EGF receptor and p53 mutations are mutually exclusive in the evolution of primary and secondary glioblastomas. *Brain Pathol* 6:217–223

3617. Waterfield MD, Scraze GT, Whittle N, Stroobant P, Johnsson A, Wasteson A, Westermark B, Heldin C-H, Huang HS, Dewell TF (1983) Platelet-derived growth factor is structurally related to the putative transforming protein p28sis of simian sarcoma virus. *Nature* 304:35–39
3618. Wattenberg LW (1983) Inhibition of neoplasia by minor dietary constituents. *Cancer Res [Suppl]* 43:2448–2453
3619. Watzka M (1943) In: *Handbuch der Mikroskopischen Anatomie des Menschen*, vol 4. Möllendorfs, Berlin
3620. Waxweiler RJ, Alexander V, Leffingwell SS (1983) Mortality for brain tumor and other causes in a cohort of petrochemical workers. *J Natl Cancer Inst* 70:75–81
3621. Waxweiler RJ, Stringer W, Wagoner JK (1976) Neoplastic risk among workers exposed to vinyl-chloride. *Ann NY Acad Sci* 271:40–48
3622. Weber HV (1935) Über Tumoren des Plexus chorioideus und deren Diagnostik. *Nervenarzt* 8:194–205
3623. Weber P, Shepard KV, Vijayakumar S (1989) Metastases to pineal gland. *Cancer* 63:164–165
3624. Wechsler W, Hossmann KA (1965) Zur Feinstruktur menschlicher Akustikusneurinoma. *Beitr Pathol Anat* 132:319–343
3625. Wechsler W, Koestner A (1972) The sequential development of transplacentally induced neuroectodermal tumors. *J Neuropathol Exp Neurol* 31:202–203
3626. Wechsler W, Meller K (1967) Electron microscopy of neuronal and glial differentiation in the developing brain of the chick. *Progr Brain Res* 26:93–144
3627. Wechsler W, Kleihues P, Matsumoto S, Zülch KJ, Ivankovic S, Preussmann R, Druckrey N (1969) Pathology of experimental neurogenic tumors chemically induced during prenatal and postnatal life. *Ann NY Acad Sci* 159:360–408
3628. Wechsler W, Ramadan MA, Gieseler A (1972) Isogenic transplantation of ethylnitrosourea-induced tumors of the central and peripheral nervous system in two different inbred rat strains. *Naturwissenschaften* 59:474–476
3629. Weichselbaum RR, Epstein J, Little JB, Kornblith PL (1976) Inherent cellular radiosensitivity of human tumors of varying clinical curability. *Amer J Roentgenol Radium Ther Nucl Med* 127:1027–1032
3630. Weil A (1933) Megalencephaly with diffuse glioblastomatosis of the brain stem and cerebellum. *Arch Neurol Psychiatry* 30:795–802
3631. Weil A, Rosenblum MP (1952) Astrocytoma of fifteen years duration. A case report. *J Neuropathol Exp Neurol* 11:409–420
3632. Weingart JD, Thompson RC, Tyler B, Colvin OM, Brem H (1995) Local delivery of the topoisomerase I inhibitor camptothecin sodium prolongs survival in the rat intracranial 9L gliosarcoma model. *Int J Cancer* 62:605–609
3633. Weingarten KL, Zimmerman RD, Leeds NE (1983) Spontaneous regression of intracerebral lymphoma. *Radiology* 149:721–724
3634. Weir B, Grace M (1976) The relative significance of factors affecting postoperative survival in astrocytomas, grades one and two. *Can J Neurol Sci* 3:47–50
3635. Weiser G (1978) Neurofibrom und Perineuralzelle. Elektronenoptische Untersuchung an 9 Neurofibromen. *Virch Arch [A] Pathol Anat* 379:73–87
3636. Weiss JF, Cravioto H, Ransohoff J (1975) Desmosterol in rat central and peripheral nervous systems during normal and neoplastic growth. Brief communication. *J Natl Cancer Inst* 54:781–783
3637. Weiss L (1955) A metastasizing ependymoma of the cauda equina. *Cancer* 8:161–171
3638. Weiss L, Sagerman RH, King GA, Chung CT, Dubowy RL (1987) Controversy in the management of optic nerve glioma. *Cancer* 59:1000–1004
3639. Weiss S, Enzinger F (1978) Malignant fibrous histiocytoma. An analysis of 200 cases. *Cancer* 41:2250–2266
3640. Weiss SW, Langloss JM, Enzinger FM (1983) Value of S-100 protein in the diagnosis of soft tissue tumors with particular reference to benign and malignant Schwann cell tumors. *Lab Invest* 49:299–309
3641. Weldon-Linne CM, Victor TA, Groothuis VR, Vick NA (1983) Pleomorphic xanthoastrocytoma. Ultrastructural and immunohistochemical study of a case with a rapidly fatal outcome following surgery. *Cancer* 52:2055–2063

3642. Wellenreuther R, Kraus JA, Lenartz D, Menon AG, Schramm J, Louis DN, Ramesh V, Gusella JF, Wiestler OD, von Deimling A (1995) Analysis of the neurofibromatosis 2 gene molecular variants of meningioma. *Am J Pathol* 146:827–832
3643. Weller RO, Griffin RL (1978) Transmission and scanning electron microscopy of the microcirculation of gliomas. In: Cervós-Navarro J, Betz E, Ebhardt G (eds) *Pathology of cerebrospinal microcirculation*. *Adv Neurol* 20:569–575
3644. Weller RO, Foy M, Cox S (1977) The development and ultrastructure of the microvasculature in malignant gliomas. *Neuropathol Appl Neurobiol* 3:303–322
3645. Weller RO, Davis BE, Wilson POG, Mitchell J (1979) Capillary proliferation in cerebral infarction, gliomas, angioblastic meningiomas, and hemangioblastomas. In: Cervós-Navarro J, Fritschka E (eds) *Cerebral microcirculation and metabolism*. Raven, New York, pp 41–48
3646. Weremowicz S, Kupsky WJ, Morton CC, Fletcher JR (1992) Cytogenetic evidence for a chromosome 22q tumor suppressor gene in ependymoma. *Cancer Genet Cytogenet* 61:193–196
3647. Werner E, Modan B, Daridoff D (1968) Doses of the brain, skull and thyroid following x-ray treatment of tinea capitis. *Phys Med Biol* 13:247–258
3648. Wernicke C, Thiel G, Lozanova T, Vogel S, Kintzel D, Jänisch W, Lehmann K, Witkowski R (1995) Involvement of chromosome 22 in ependymomas. *Cancer Genet Cytogenet* 79:173–176
3649. Werteleki W, Rouleau GA, Supernau DW, Forehand LW, Williams JP, Haines JL, Gusella JF (1988) Neurofibromatosis 2: clinical and DNA linkage studies of a large kindred. *New Engl J Med* 319:278–283
3650. Wertheimer N, Leper E (1982) Adult cancer related to electrical wires near the home. *Int J Epidemiol* 11:345–355
3651. Wesseling P, Van der Laak JAWM, de Leeuw H, Ruiter DJ, Burger PC (1994) Quantitative immunohistological analysis of the microvasculature in untreated human glioblastoma multiforme. *J Neurosurg* 81:902–909
3652. West CR, Bruce DA, Duffner PK (1985) Ependymomas: factors in clinical and diagnostic staging. *Cancer* 56:1812–1816
3653. West SG, Pittman DL, Coggin JT (1980) Intracranial plasma cell granuloma. *Cancer* 46:330–335
3654. Westphal M, Stavron D, Nausch H, Valdueza JM, Herrmann H-D (1994) Human neurocytoma cells in culture show characteristics of astroglial differentiation. *J Neurosci Res* 38:698–704
3655. Wettler H (1948) Das intrakranielle Epidermoid. *Mschr Psychiatr Neurol* 115:233–276
3656. Wharen RE Jr, Anderson RE, Laws ER Jr (1983) Quantitation of hematoporphyrin derivative in human gliomas, experimental central nervous system tumors, and normal tissue. *Neurosurgery* 12:446–450
3657. Wharen RE Jr, Anderson RE, Laws ER Jr (1991) Photoradiation therapy of brain tumors. In: Salzman M (ed) *Neurobiology of brain tumors*. Williams and Wilkins, Baltimore, pp 341–357
3658. Wheeler KT, Deen DF, Wilson CB, Williams ME, Sheppard ME, Sheppard S (1977) BCNU-modification of in vitro response in 9L brain tumor cells of rats. *Int J Radiat Oncol Biol Phys* 2:79–84
3659. Wheeler KT, Kaufman K, Feldstein M (1979) Response of a rat brain tumor to fractionated therapy with low doses of BCNU and irradiation. *Int J Radiat Oncol Biol Phys* 5:1553–1557
3660. Wheeler KT, Wallen CA (1980) Is cell survival a determinant of the in situ response of 9L tumours? *Br J Cancer* 41:299–303
3661. Wheeler KT, Kaufman K (1981) Efficacy of continuous treatment with radiation in a brain tumor model. *J Neurosurg* 55:52–54
3662. Wheeler KT, Kaufman K (1981) Brain tumor therapy: prospects for combining BCNU with conventional radiotherapy schedules. *Int J Radiat Oncol Biol Phys* 7:1065–1068
3663. Wheldon TE, O'Donoghue JA (1990) The radiobiology of targeted radiotherapy. *Int J Radiat Biol* 58:1–21
3664. Whitaker SJ, Bessell EM, Ashley SE, Bloom HJG, Bell BA, Brada M (1991) Postoperative radiotherapy in the management of spinal cord ependymoma. *J Neurosurg* 74:720–728
3665. White KT, Fleming TR, Laws ER Jr (1981) Single metastasis to the brain. Surgical treatment in 122 consecutive patients. *Mayo Clin Proc* 56:424–428
3666. Whiteside TL (1982) Reactivity of antihuman brain serum with human lymphocytes. *Am J Pathol* 86:1–16

3667. Whitton AC, Bloom HJG (1990) Low grade glioma of the cerebral hemispheres in adults: a retrospective analysis of 88 cases. *Int J Radiat Oncol Biol Phys* 18:783-786
3668. Whyte P, Buchkovich KJ, Horowitz JM, Friend SH, Raybuck M, Weiberg RA, Harlow E (1988) Association between an oncogene and an anti-oncogene: the adenovirus E1A proteins bind to the retinoblastoma gene product. *Nature* 334:124-129
3669. Wiedenmann B, Franke WW (1985) Identification and localization of synaptophysin, an integral membrane glycoprotein of Mr 38000 characteristic of presynaptic vesicles. *Cell* 41:1017-1028
3670. Wiestler OD, Kleihues P, Pegg AE (1984) O6 alkylguanine-DNA alkyltransferase activity in human brain and brain tumors. *Carcinogenesis* 5:121-124
3671. Wiestler OD, Brüstle O, Eibel RH, Radner H, Aguzzi A, Kleihues P (1992) Retrovirus-mediated oncogene transfer into neural transplants. *Brain Pathol* 2:47-59
3672. Wiestler OD, von Siebenthal K, Schmitt HP, Fliden DW, Kleihues P (1989) Distribution and immunoreactivity of cerebral micro-hamartomas in bilateral acoustic neurofibromatosis (neurofibromatosis 2). *Acta Neuropathol (Berl)* 79:137-143
3673. Wikstrand CJ, Bigner DD (1980) Immunologic aspect of the brain and human gliomas. *Am J Pathol* 98:517-567
3674. Wikstrand CJ, Bigner SH, Bigner DD (1983) Demonstration of complex antigenic heterogeneity in a human glioma cell line and eight derived clones by specific monoclonal antibodies. *Cancer Res* 43:3327-3334
3675. Wikstrand CJ, Bourdon MA, Pegram CN, Bigner DD (1982) Human fetal brain antigen expression common to tumors of neuroectodermal tissue origin. *J Neuroimmunol* 3:43-62
3676. Wikstrand CJ, Grahmann FC, McComb RD, Bigner D (1986) Antigenic heterogeneity of human glioma tissue and cell lines (HGL) defined by monoclonal antibodies (MAbs) In: Walker MD, Thomas DGT (eds) *Biology of brain tumours*. Nijhoff, Boston, pp 495-499
3677. Wilkins HV, Rutledge BJ, (1961) Papillomas of the choroid plexus. *J Neurosurg* 18:14-18
3678. Wilkins JR, Sinks T (1990) Parietal occupation and intracranial neoplasms of childhood: results of a case-control interview study. *Am J Epidemiol* 132:275-292
3679. Wilkins RH (1985) Natural history of intracranial vascular malformations: a review. *Neurosurgery* 16:421-430
3680. Wilkinson IMS, Anderson JR, Holmes AE (1987) Oligodendroglioma: an analysis of 42 cases. *J Neurol Neurosurg Psychiatry* 50:304-312
3681. Willbeyer JE (1989) Primary intrasellar Schwannoma: case report. *Surg Neurol* 31:156-158
3682. Williams BO, Remington I, Albert DM, Mukai S, Bronson RT, Jacks T (1994) Cooperative tumorigenic effects of germeline mutations in Rb and p53. *Nature Genet* 7:480-484
3683. Williams JM, Fox JL (1962) Neurinoma of the intracranial portion of the hypoglossal nerve. Review and case report. *J Neurosurg* 19:248-250
3684. Williams PC, Henner WD, Romangoldstein S, Dahlborg SA, Brummett RE, Tableman M, Dana BW, Neuwelt EA (1995) Toxicity and efficacy of carboplatin and etoposide in conjunction with disruption of the blood-brain tumor barrier in the treatment of intracranial neoplasms. *Neurosurgery* 37:17-27
3685. Williams RS, Crowell RM, Fisher CM, Davis K, Lavyne MH, Ropper AM, Bremer AM (1979) Clinical and radiologic remission in reticulum cell sarcoma of the brain. *Arch Neurol* 36:206-210
3686. Willis RA (1952) *The spread of tumors in the human body*, 2nd edn. Butterworth, London
3687. Willis RA (1971) Secondary tumors. In: Minckler J (ed) *Pathology of the nervous system*, vol 2. McGraw-Hill, New York, p 2178
3688. Willson N, Duffy PE (1974) Morphologic changes associated with combined BCNU and radiation therapy in glioblastoma multiforme. *Neurology* 24:465-471
3689. Wilson AJ, Leaffer DH, Kohout ND (1985) Differentiated cerebral neuroblastoma: a tumor in need of discovery. *Hum Pathol* 16:647-649
3690. Wilson CB (1978) Brain tumor models for experimental therapy. In: Laerum OD, Bigner DD, Rajewsky MF (eds) *Biology of brain tumors*. UICC Techn Rep Ser 26:185-196
3691. Wilson CB (1994) Meningiomas: genetics, malignancy, and the role of radiation in induction and treatment. *J Neurosurg* 81:666-675
3692. Wilson WB, Feinsod M, Hoyt WF, Nielsen SL (1976) Malignant evolution of childhood chiasmal pilocytic astrocytoma. *Neurology* 26:322-325

3693. Winek RR, Scheithauer BW, Wick MR (1989) Meningioma, meningeal hemangiopericytoma (angioblastic meningioma), peripheral hemangiopericytoma and acoustic schwannoma: a comparative immunohistochemical study. *Am J Surg Pathol* 13:251–261
3694. Winger MJ, Mac Donald DR, Cairncross JG (1989) Supratentorial anaplastic gliomas in adults. The prognostic importance of extent resection and prior low-grade glioma. *J Neurosurg* 71:487–493
3695. Wingren G, Axelson O (1985) Mortality pattern in a glass producing area of SE Sweden. *Brit J Ind Med* 42:411–414
3696. Winkelman NW, Cassel C, Schlesinger B (1952) Intracranial tumors with extracranial metastases. *J Neuropathol Exp Neurol* 11:149–166
3697. Winship T, Klopp CT, Jenkins WH (1948) Glomus-jugularis tumors. *Cancer* 1:441–448
3698. Winston K, Gilles F, Leviton A, Fulcher A (1977) Cerebellar gliomas in children: clinical considerations and a proposed classification. *J Natl Cancer Inst* 58:833–838
3699. Winston KR, Sotrel A, Schmitt SJ (1987) Meningeal melanocytoma: a case report and review of the clinical and histological features. *J Neurosurg* 66:50–57
3700. Winston M, Johnson E, Kelleher JK (1974) Melatonin: cellular effects on live stentors correlated with the inhibition of colchicine-binding to microtubule protein. *Cytobios* 9:237–243
3701. Wisoff HS, Llena JF (1989) Glioblastoma multiforme of the cerebellum five decades after irradiation of a cerebellar tumor. *J Neurooncol* 7:339–344
3702. Wisoff JH, Abbott R, Epstein F (1990) Surgical management of exophytic chiasmatic-hypothalamic tumors in childhood. *J Neurosurg* 73:661–667
3703. Wissler JH (1982) In: Jaenicke L (ed) *Biochemistry of differentiation and morphogenesis*. Springer, Berlin Heidelberg New York, pp 257–274
3704. Witzmann A, Jellinger K, Weis R (1981) Glioblastoma multiformenach Kopfschuss. *Neurochirurgia* 24:202–206
3705. Wixon HN, Hunt HN (1983) Ionizing radiation decrease veratridine-stimulated uptake of sodium in rat brain synaptosomes. *Science* 220:1073–1074
3706. Wohlwill FJ, Yakovlev PI (1957) Histopathology of meningo-facial-angiomatosis (Sturge-Weber's disease). *J Neuropathol Exp Neurol* 16:341–364
3707. Wolf HK, Müller MB, Spänle M, Zentner J, Schramm J, Wiestler OD (1994) Ganglioglioma: a detailed histopathological and immunohistochemical analysis of 61 cases. *Acta Neuropathol (Berl)* 88:166–173
3708. Wolman L (1953) The origin of the fibrous tissue in meningiomata. *J Neuropathol Exp Neurol* 12:194–200
3709. Wolman L, Balmforth GV (1963) Precocious puberty due to a hypothalamic hamartoma in a patient surviving to late middle age. *J Neurol Neurosurg Psychiatry* 26:275–280
3710. Woltman HW, Kernohan JW, Adson AW, Mc Craig W (1951) Intramedullary tumors of spinal cord and gliomas of intradural portion of filum terminale. Fate of patients who have these tumors. *Arch Neurol Psychiatry* 65:378–395
3711. Wong AJ, Bigner SH, Bigner DD, Kinzler KW, Hamilton SR, Vogelstein B (1987) Increased expression of the EGF receptor gene in malignant glioma is invariably associated with gene amplification. *Proc Natl Acad Sci USA* 84:6899–6903
3712. Wong AJ, Ruppert JM, Bigner SH, Grzeschik CH, Humphrey PA, Bigner DS, Vogelstein B (1992) Structural alterations of the epidermal growth factor receptor gene in human gliomas. *Proc Natl Acad Sci USA* 89:2965–2969
3713. Wong JY, Uhl V, Wara WM, Sheline GE (1987) Optic gliomas. A reanalysis of the University of California, San Francisco experience. *Cancer* 60:1847–1855
3714. Wood GW, Morantz RA (1979) Immunohistologic evaluation of the lymphoreticular infiltrate of human central nervous system tumors. *J Natl Cancer Inst* 62:485–491
3715. Wood JR, Green SB, Shapiro WR (1988) The prognostic importance of tumor size in malignant gliomas: a computed tomography scan study by the Brain Tumor Cooperative Group. *J Clin Oncol* 6:338–342
3716. Wood MW, Robert JW, Kernohan JW (1957) One hundred intracranial meningiomas found incidentally at necropsy. *J Neuropathol Exp Neurol* 16:337–340
3717. Woodman R, Shin K, Pineo G (1985) Primary non-Hodgkin's lymphoma of the brain. A review. *Medicine* 64:425–430

3718. Woodruff JM, Christensen WN (1993) Glandular peripheral nerve sheath tumors. Comments. *Cancer* 72:3618–3628
3719. Woodruff JM, Godwin TA, Erlandson RA, Susin M, Martini M (1981) Cellular Schwannoma. A variety of Schwannoma sometimes mistaken for a malignant tumor. *Am J Surg Pathol* 5:733–744
3720. Worster-Drought C, Carnegie Dickson WE, McMenemey WH (1937) Multiple meningeal and perineural tumours with analogous changes in the glia and ependyma (neurofibromatosis). *Brain* 60:85–117
3721. Wrensch M, Bondy M, Wiencke J, Yost M (1993) Environmental risk factors for primary malignant brain tumors. *J Neurooncol* 17:47–64
3722. Wright JE, Call NB, Liaricos S (1980) Primary optic nerve meningioma. *Br J Ophthalmol* 64:553–558
3723. Wronski M, Arbit E, Burt M, Galicich JH (1995) Survival after surgical treatment of brain metastases from lung cancer: A follow-up study of 231 patients treated between 1976 and 1991. *J Neurosurg* 83:605–616
3724. Wu JK, Ye Z, Darras BT (1993) Frequency of p53 tumor suppressor gene mutations in human primary brain tumors. *Neurosurgery* 33:824–830
3725. Wullich B, Muller HW, Fischer U, Zang KD, Meese E (1993) Amplified met gene linked to double minutes in human glioblastoma. *Eur J Cancer* 14:1991–1995
3726. Wurtman RJ, Moskowitz MA (1977) The pineal organ, parts I and II. *New Engl J Med* 296:1329–1333, 1383–1386
3727. Wyatt RB, Schochet SS, McCornick WF (1971) Echordosis physaliphora. An electron microscopic study. *J Neurosurg* 34:672–677
3728. Wyburn-Mason R (1943) Arteriovenous aneurism of mid-brain and retina, facial naevi and mental changes. *Brain* 66:163–171
3729. Wyburn-Mason R (1943) The vascular abnormalities and tumours of the spinal cord and its membranes. Kimpton, London
3730. Wycis HT (1948) Oligodendroglioma of the cerebellum. *Arch Neurol Psychiatry* 69:404–407
3731. Wyllie AH, (1985) The biology of cell death in tumors. *Anticancer Res* 5:131–136
3732. Wyllie AH (1992) Apoptosis and the regulation of cell numbers in normal and neoplastic tissues: and overview. *Cancer Metastasis Rev* 11:95–103
3733. Wyllie AH (1993) Apoptosis (the 1992 Frank Rose memorial lecture). *Br J Cancer* 67:205–208
3734. Xu G, O'Connell P, Viskochil D, Cawthon R, Robertson M, Culver M, Dunn D, Stevens J, Gesteland R, White R, Weiss R (1990) The neurofibromatosis type 1 gene encodes a protein related to GAP. *Cell* 62:599–608
3735. Xu W, Mulligan LM, Ponder MA, Liu L, Smith BA, Mathew CGP, Ponder BAJ (1992) Loss of NF1 alleles in pheochromocytomas from patients with type 1 neurofibromatosis. *Genes Chrom Cancer* 4:337–342
3736. Yachnis AT, Rorke LB, Perilongo G (1991) Desmoplastic primitive neuroectodermal tumor with divergent differentiation: broadening the spectrum of desmoplastic infantile neuroepithelial. *J Neuropathol Exp Neurol* 50:292
3737. Yachnis AT, Rorke LB, Lee VM-Y, Trojanowski JQ (1993) Expression of neuronal and glial polypeptides during histogenesis of the human cerebellar cortex including observations on the dentate nucleus. *J Comp Neurol* 334:356–369
3738. Yachnis AT, Rorke LB, Trojanowski JQ (1994) Cerebellar dysplasias in humans: development and possible relationship to glial and primitive neuroectodermal tumors of the cerebellar vermis. *J Neuropathol Exp Neurol* 53:61–71
3739. Yagishita S, Itoh Y, Chiba Y, Kuvana N (1982) Morphological investigations on cerebellar "neuroblastoma" group. *Acta Neuropathol (Berl)* 56:22–28
3740. Yagishita S, Itoh Y, Shiozawa T, Tanaka T (1984) Ultrastructural observation on a colloid cyst of the third ventricle. A contribution to its pathogenesis. *Acta Neuropathol (Berl)* 65:41–45
3741. Yalcin S, Fragoyannis S (1966) Intracranial lipoma. Case report. *J Neurosurg* 24:895–897
3742. Yamada K, Hayakawa T, Ushio Y, Arita N, Kato A, Mogami H (1981) Regional blood flow and capillary permeability in the ethylnitrosourea-induced rat glioma. *J Neurosurg* 55:922–928
3743. Yamadori I (1985) Developmental behavior of N,N-dimethylnitrosourea-induced brain gliomas and influence of a stab wound in adult rats. *Acta Pathol Jpn* 35:1201–1213



3744. Yamagami T, Handa H, Takechi J, Niiijima K, Furukawa F (1983) Choriocarcinoma arising from pituitary fossa with extracranial metastasis: a review of the literature. *Surg Neurol* 19:462–480
3745. Yamasaki T, Yamasaki J, Wanda H, Watanabe Y, Naba Y, Hanadka M (1984) Specific adoptive immunotherapy with tumor specific cytotoxic T lymphocyte clone for murine malignant gliomas. *Cancer Res* 44:1776–1783
3746. Yasargil MG, Abernathy CD, Sariogla AL (1982) Microneurosurgical treatment of intracranial dermoid and epidermoid tumors. *Neurosurgery* 24:5617
3747. Yasargil MG, von Ammon K, von Deimling A, Valavanis A, Wichmann W, Wiestler OD (1992) Central neurocytoma: histological variants and therapeutic approaches. *J Neurosurg* 76:32–37
3748. Yasunaga T, Takahashi M, Uozumi H, Kazami T (1986) Radiation therapy of primary malignant lymphoma of the brain. *Acta Radiol (Oncol)* 25:23–28
3749. Yates AJ, Becker LE, Sachs LA (1979) Brain tumors in childhood. *Childs Brain* 5:31–39
3750. Yeh HJ, Ruit KG, Wang YX, Parks WC, Snider WD, Deuel TF (1991) PDGF A-chain gene is expressed by mammalian neurons during development and in maturity. *Cell* 64:209–216
3751. Yeh HJ, Silos-Santiago I, Wang YX, George RJ, Snider WD, Deuel TF (1993) Developmental expression of the platelet-derived growth factor  $\alpha$ -receptor gene in mammalian central nervous-system. *Proc Natl Acad Sci* 90:1952–1956
3752. Yin Y, Tainsky MA, Bischoff FZ, Strong LC, Wahl GM (1992) Wild-type cellcycle control and inhibits gene amplification in cells with mutant p53 alleles. *Cell* 70:937–948
3753. Yong WH, Chou D, Ueki K, Harsh IV GR, von Deimling A, Gusella JF, Mohrenweiser HW, Louis ND (1995) Chromosome 19q deletions in human gliomas overlap telomeric to D19S219 and may target a 425 kb region centromeric to D19S112. *J Neuropathol Exp Neurol* 54:622–626
3754. Yoshida J, Kobayashi T, Kageyama N, Kauzaky M (1977) Symptomatic Rathke's cleft cyst. Morphological study with light and electron microscopy and tissue culture. *J Neurosurg* 47:451–458
3755. Yoshida J, Yamamoto R, Wakabayashi T, Nagata M, Seo H (1990) Radioimmunoassay of glioma-associated antigen in cerebrospinal fluid and its usefulness for the diagnosis and monitoring of human glioma. *J Neurooncol* 8:23–31
3756. Yoshida T, Ushio Y, Hayakawa T, Yamada K, Mogami H, Nakata Y (1984) Development of ACNU-resistant meningeal gliomatosis models: establishment of resistant rat glioma sublines against ACNU. *Neurol Surg* 12:1029–1036
3757. Yoshida T, Shimizo IC, Ushio Y, Mogami H, Sakamoto Y (1987) Modulation in vitro and in vivo of ACNU resistance in a subline of C6 glioma with reserpine. *J Neurosurg* 66:251–255
3758. Yoshida T, Shimizu K, Ushio Y, Hayakawa T, Mogami H, Sakamoto Y (1987) The mechanism and overcoming of resistance in ACNU-resistant sublines of C6 and 9L rat glioma. *J Neurooncol* 5:195–203
3759. Yoshiki T, Itoh T, Shirai T, Noro T, Tomino Y, Hamajima I, Takeda T (1976) Primary intracranial yolk sac tumor. Immunofluorescent demonstration of alpha-fetoprotein synthesis. *Cancer* 37:2343–2348
3760. Young RH, Kleinman GM, Scully RE (1981) Glioma of the uterus. Report of a case with comments on histogenesis. *Am J Surg Pathol* 5:695–699
3761. Younis GA, Sawaya R, DeMonte F, Hess KR, Albrecht S, Bruner JM (1995) Aggressive meningeal tumors: review of a series. *J Neurosurg* 82:17–27
3762. Yu CCW, Filipe I (1993) Update on proliferation-associated antibodies applicable to formalin-fixed paraffin embedded tissue and their clinical applications. *Histochem J* 25:843–853
3763. Yu ZY, Wrangle O, Haglund B, Granholm L, Gustafsson JA (1982) Estrogen and progesterone receptors in intracranial meningiomas. *J Steroid Biochem* 16:451–456
3764. Yuan J, Shaham S, Ledoux S, Ellis HM, Horvitz HR (1993) The *C. elegans* cell death gene *ced-3* encodes a protein similar to mammalian interleukin-1 $\beta$ -Converting Enzyme. *Cell* 75:641–652
3765. Yuhas JM, Afzal MJ, Afzal V (1984) Variation in normal tissue responsiveness to WR-2721. *Int J Radiat Oncol Biol Phys* 10:1537–1539
3766. Yuile CL (1938) Case of primary reticulum cell sarcoma of the brain: relation of microglia cells to histiocytes. *Arch Pathol* 26:1036–1045

3767. Yung WKA, Horten BC, Shapiro WR (1980) Meningeal gliomatosis. A review of 12 cases. *Ann Neurol* 8:605–608
3768. Yung WKA, Shapiro JR, Shapiro WR (1982) Heterogeneous chemosensitivities of subpopulations of human glioma cells in culture. *Cancer Res* 42:992–998
3769. Yung WKA, Fine H, Martuza R (1995) Report from the National CNS Tumor Consortium (N CNCSC). In: 11th International Conference of Brain Tumor Research and Therapy, 31 October–3 November, Silverado, Ca
3770. Zack M, Cannon S, Loyd D (1980) Cancer in children of parents exposed to hydrocarbon-related industries and occupations. *Am J Epidemiol* 111:329–366
3771. Zagzag D, Miller DC, Sato Y, Rifkin DB, Burstein DE (1990) Immunohistochemical localization of basic fibroblast growth factor in astrocytomas. *Cancer Res* 50:7393–7398
3772. Zanker KS, Stavrou D, Osterkamp U, Wriedt-Lübbe I, Blümel G (1978) Fibrinolysis induced by rat glioma cells. *J Neurol Sci* 38:67–75
3773. Zankl H, Zang KD (1980) Correlations between clinical and cytogenetical data in 180 human meningiomas. *Cancer Genet Cytogenet* 1:351–356
3774. Zbar B, Hosoe S, Brauch H, Latif F, Glenn G, Daniel L, Bale S, Choyke P, Gorin M, Oldfield E, Berman A, Goodman J, Orcutt ML, Hampsch K, Delisio J, Modi W, McBride W, Linehan M, Lerman M (1991) Close linkage of the von Hippel-Lindau disease gene to a highly polymorphic marker located at 3p26. *Am J Hum Genet* 47:A205
3775. Zeman W (1963) Disturbances of nucleic acid metabolism preceding delayed radionecrosis of nervous tissue. *Proc Natl Acad Sci USA* 50:626–630
3776. Zeman W, Shidnia H (1976) Post-therapeutic radiation injures of the nervous system. Reflections on their prevention. *J Neurol* 212:107–115
3777. Zenker FA (1857) Enorm Cystenbildung im Gehirn, vom Hirnanhang ausgehend. *Arch Pathol Anat Physiol Klin Med* 2:454–466
3778. Zentner J, Wolf HK, Ostertum B, Hufnagel A, Campos MG, Solymosi L, Schramm J (1994) Gangliogliomas: clinical, radiological, and histopathological findings in 51 patients. *J Neurol Neurosurg Psychiatry* 57:1497–1502
3779. Zerbini C, Gelber RD, Weinberg D, Sallan SE, Barnes P, Kupsky W, Scott RM, Tarbell NJ (1993) Prognostic factors in medulloblastoma, including DNA ploidy. *J Clin Oncol* 4:616–622
3780. Zervas NT, Shintani A, Kallar B, Berry RG (1970) Multiple meningiomas occupying neuraxial compartments. *J Neurosurg* 33:216–220
3781. Zettner A, Netsky MG (1960) Lipoma of the corpus callosum. *J Neuropath Exp Neurol* 19:305–319
3782. Zhang S, Feng X, Koga H, Ichikawa T, Abe S, Kumanishi T (1993) p53 gene mutations in pontine gliomas of juvenile onset. *Biochem Biophys Res Commun* 196:851–857
3783. Zhang W, Yamada H, Sakai U (1993) Sensitization of C6 glioma cells to radiation by staurosporine, a potent protein kinase C inhibitor. *J Neurooncol* 15:1–7
3784. Ziche M, Jones J, Gullino PM (1982). Role of prostaglandin E 1 and copper in angiogenesis. *J Natl Cancer Inst* 62:475–482
3785. Zimmerman BL, Tso MOM (1975) Morphologic evidence of photoreceptor differentiation of pinealocytes in the neonatal rat. *J Cell Biol* 66:60–75
3786. Zimmerman HM (1962) Experimental brain tumors. In: Fields WS, Sharkey PC (eds) *The biology and treatment of intracranial tumors*. Thomas, Springfield, pp 49–56
3787. Zimmerman HM (1969) Brain tumours: their incidence and classification in man and their experimental production. *Ann NY Acad Sci* 159:337–359
3788. Zimmerman HM, Arnold H (1941) Experimental brain tumors. I. Tumors produced by methylcolantrene. *Cancer Res* 1:919–938
3789. Zimmerman HM, Arnold H (1943) Experimental brain tumors. II. Tumors produced with benzpyrene. *Am J Pathol* 19:939–955
3790. Zimmerman RA (1990) Central nervous system lymphoma. *Radiol Clin N Am* 28:697–721
3791. Zimmerman RD, Fleming CA, Saint-Louis LA, Lee BCP, Manning JJ, Deck MDF (1985) Magnetic resonance imaging of meningiomas. *AJNR* 6:149–157
3792. Zito JL, Siva A, Smith TW, Leeds M, Davidson R (1983) Glioblastoma of the cerebellum. Computed tomographic and pathologic considerations. *Surg Neurol* 19:373–378
3793. Zook BC, Bradley EW, Casarett GW, Rubin P (1980) Pathologic findings in canine brain irradiated with fractionated fast neutrons or photons. *Radiat Res* 84:562–578

3794. Zorzi F (1987) Xantoastrocitoma pleomorfo cerebro-meningeo. *Quaderni di Neuropatologia* 3:45–57
3795. Zuber P, Hamou ME, de Tribolet N (1988) Identification of proliferating cells in human gliomas using the monoclonal antibody Ki-67. *Neurosurgery* 22:364–368
3796. Zülch KJ (1937) On the question of cerebellar astrocytomas. *Zbl Neurochir* 2:360–371
3797. Zülch KJ (1940) Hirngeschwülste im Jugendalter. *Zbl Neurochir* 5:238–274
3798. Zülch KJ (1941) Ein Medulloblastom mit glatten Muskelfasern. *Arch Psychiatr Nervenkr* 114:349–352
3799. Zülch KJ (1956) Biologie und Pathologie der Hirngeschwülste. In: Zülch KJ, Christensen E (eds) *Pathologische Anatomie der raumbeengenden intrakraniellen Prozesse*. Springer, Berlin
3800. Zülch KJ (1962) The present state of the classification on intracranial tumours and its value for the neurosurgeon. In Fields WS, Sharkey PC (eds) *The biology and treatment of intracranial tumors*. Thomas, Springfield, pp 157–177
3801. Zülch KJ (1965) *Brain tumours. Their biology and pathology*, 2nd edn. Springer, Berlin Heidelberg New York
3802. Zülch KJ (1979) Histological typing of tumours of the central nervous system. *International Histological Classification of Tumours*, no 21. World Health Organization, Geneva
3803. Zülch KJ (1986) *Brain tumors. Their biology and pathology*, 3rd edn. Springer, Berlin Heidelberg New York
3804. Zülch KJ, Mennel H (1971) Die Morphologie der durch alkylierende Substanzen erzeugten Tumoren des Nervensystems. *Zbl Neurochir* 32:225–243
3805. Zülch KJ, Schmid EE (1955) Über das Ependymom der Seitenkammern am Foramen Monro. *Arch Psychiatr Nervenkr* 193:214–228
3806. Zülch KJ, Wolf AL (1964) *Classification of the brain tumors*. Springer, Vienna
3807. Zúñiga OF, Tanner SM, Wild WO et al (1983) Hamartoma of CNS associated with precocious puberty. *Am J Dis Child* 137:127–133

---

## Subject Index

- A2B5 cells 5, 8, 110, 130, 223  
Ag-NORs 119  
AIDS 33, 494  
alpha-fetoprotein (AFP) 71, 419  
anaplasia 99–101, 109–115  
    in astrocytoma 147, 148, 151  
    in meningioma 359–362  
    in oligodendroglioma 223–226  
angiogenesis in gliomas 178–185  
angiogenin 184  
anti-Leu-M1 66  
antigens  
    brain tumor-associated 56, 57  
    of phenotypic expression 56–73  
apoptosis 22, 81, 121, 122, 291  
arachnoid cyst 462  
arteriovenous malformations 483  
astroblastoma 196  
astrocytes type 1 and 2 5, 17  
astrocytoma 139–155  
    anaplastic (malignant) transformation  
        147, 150, 151, 211  
    anaplastic variant 138, 147–149  
    of brain stem 201–203  
    of cerebellum 203–212  
    of cerebral hemispheres 139–155  
    of chiasm 199, 200  
    fibrillary variant 138–140  
    gemistocytic variant 138  
    of midline 197  
    of optic nerve 198  
    pilocytic variant 138, 142–147, 205–209  
    of pineal region 276  
    protoplastic variant 138, 141, 142  
    of spinal cord 213  
ataxia teleangiectasia 483  
atypia, cellular 109, 112  
autoradiography 116, 117  
Avian Sarcoma Virus (ASV) 52  
  
bcl.2 24, 121, 122  
Bergmann's glia 4, 11  
beta-tubulin 11, 268, 303–305  
blood brain barrier (BBB) 83–85  
brachithrapy 509, 510  
  
bromodeoxyuridin (BrdU) 116, 117, 119, 120,  
    130, 150, 185  
Bourneville's disease 475–477  
  
c-fos 121  
c-jun 121  
c-myc 27, 28, 115, 121  
c-sis 28  
C6 glioma 54  
Cajal-Retzius cells 4  
calbindin 11, 304  
calcifications 89–92, 482  
    in astrocytoma 140, 146  
    in craniopharyngioma 92  
    in oligodendroglioma 216–221  
    in pilocytic astrocytoma 206  
carbonic anhydrase C 61, 223  
carcinoembryonic antigen (CEA) 256, 419  
carcinomatous meningitis 505  
CD31 66  
cell kinetics 115–122  
cerebellar hemangioblastoma 481  
cerebral edema 83–88  
chemical carcinogenesis 39–55  
    resorptive carcinogens 39–52  
    topically acting carcinogens 39  
chemodectoma 319–321  
chemoresistance in brain tumors 513–516  
chemosensitivity in brain tumors 513–516  
chemotherapy 513–519  
    with BBB modification 518  
    biological basis 513–519  
    with carrier systems and liposomes  
        518, 519  
    effects on human brain and spinal cord  
        534  
    effects on human brain tumor  
        522, 523  
    general concepts 513  
    of glioblastoma 188, 189  
    high-dose 517  
    interstitial 517  
    intra-arterial 517  
    intra CSF 517  
    of lymphoma 497

- chemotherapy
  - of medulloblastoma 307
  - of oligodendroglioma 227
- chondroma 397, 398
- chondrosarcoma 398
- chordoma 392
  - origin 392
- chorioncarcinoma 417
- choristoma 465
- chromaffin cells 319
- chromogranin 65, 321
- chromosomal abnormalities
  - in gliomas 24
  - in medulloblastoma 26
  - in neurofibromatosis 21
  - in retinoblastoma 19
- ciliary neurotrophic factor 7, 16
- classification of neuroepithelial tumors 96–106
- colloid cysts 457, 459
- congenital tumors 135
- cortical plate 3
- craniopharyngeal duct 435
- craniopharyngioma 435–459
  - adamantinomatous areas 445
  - calcifications 450
  - cysts 451
  - intraventricular 439
  - keratinization 445, 449
  - prognosis 458
  - treatment 456
- cytokeratin 68, 73
- cytophotometry 113, 116
- dedifferentiation 109
- dermo-epidermoid cyst 430–435
- desmin 69
- desmoplastic infantile astrocytoma 267, 268
- differentiation 110
  - markers 58–66
- double minutes 26
- drug delivery to brain tumors 516, 517
- dysembryoplastic neuroepithelial tumors 270–272
- dysplasia 481
- dysplastic gangliocytoma of the cerebellum 266
- ecchordosis physaliphora 392
  - immunohistochemistry 396
  - physaliphorous cells 393
  - sacrococcygeal 395
  - vertebral 395
- ectodermal matrix 2
- ectopic gliomas 468
- elongin 22
- embryonal carcinoma 417
- endodermal sinus tumor 417
- endothelial cells immunohistochemistry 66
- endothelial hyperplasia
  - in anaplastic astrocytoma 147
  - in ependymoma 235
  - in glioblastoma 162, 178, 179
  - in medulloblastoma 291
  - in pilocytic astrocytoma 206
- enterogeneous cyst 462
- eosinophilic granular bodies 146
- ependyma 11
  - turnover 14
- ependymal layer 4
- ependymoblastoma 252, 253
- ependymoma 228–249, 480
  - anaplastic variant 245–247
  - cellular 228, 233
  - epithelial 228, 235
  - extraspinal 231
  - grading 245
  - immunohistochemistry 239–242
  - mixopapillary variant 228, 233, 239, 249
  - papillary 228, 235
  - prognostic factors 248
  - regressive events 237–239
  - spreading 248
  - treatment 248, 249
- epidemiology of cerebral tumors 132–136
  - of brain tumors in children 135
  - of spinal tumors 136
- epidermal growth factor (EGF) 26, 130
- epidermal growth factor receptor (EGFR) 26, 27
  - gene amplification 112
  - in glioblastoma 165
- epithelial membrane antigen (EMA) 71
- esthesioneuroepithelioma 272–274
- ethylnitrosourea-induced tumors (ENU) 39–48, 52
  - induced-tumors 41–52
  - cell composition 48–50
  - early neoplastic proliferations 41, 44
  - microtumors 48
  - pathogenesis 46–48
  - reactive astrocytes 48
  - vascularization 51
- external granular layer 10, 300, 304
- extracellular matrix 130, 131
- factor VIII related antigen (FVIII/RAG) 66, 173, 179, 410
- Fahr's disease 90
- fas antigen 121, 122
- fibroblast growth factor (FGF) 29, 130, 180, 183, 185
- fibronectin 66, 488
- fibrosarcoma 386

- fibrous histiocytoma 382
  - malignant 386
- fleurettes 282, 315, 318
- Flexner Wintersteiner rosettes 282
- flow cytometry 113, 116, 119
- galactocerebroside (GC) 221
- gangliocytoma 260, 264
- ganglioglioma 260–266
  - immunohistochemistry 264
  - malignant variant 264, 265
- ganglioneuroblastoma 308
- ganglioneuroma 478
- gene transfer models of brain tumors 54
- genetics of brain tumors 18–29
- genotypic heterogeneity 112
- germ cell tumors 412
  - origin 413
- germinal cells 2–4
  - cell cycle 3
- germinal zone 4, 8, 10
- germinoma 414
  - histology 415
  - therapy 416
- glial fibrillary acidic protein (GFAP) 60–61, 66, 68
  - and anaplasia 113
  - in central neurocytoma 268
  - during CNS development 3, 4, 7
  - in ependyma 14
  - in ependymoma 239–242
  - in glioblastoma 165, 169
  - in gliosarcoma 172, 173
  - in glomus tumors 321
  - in medulloblastoma 300
  - in neurinoma 333
  - in oligodendroglioma 221
  - in pilocytic astrocytoma 146, 205
  - in plexus papilloma 256
  - in radial glia 11
  - in reactive astrocytes 74, 76, 78, 79
  - in retinoblastoma 315, 318
  - in Rosenthal fibres 209
  - in tuberous sclerosis 194
  - in xanthoastrocytoma 192
- glial differentiation 4–7, 11–14, 17
- glial markers 58–63
- glial reaction 74–79
  - in glioblastoma 164, 165
  - subependymal 79
- glial turnover 8, 9
- glioblastoma multiforme 155–171
  - of the cerebellum 211
  - endothelial proliferation 162, 178, 179
  - giant cell variant 171
  - primary and secondary 26, 27, 112
  - spreading 169, 170
- glioblasts 5
- gliofibroma 178
- gliogenesis 2–11
  - in adult animals 8–10
  - in cerebellum 10–11
- gliomatosis cerebri 189, 190
- gliosarcoma 172–178
  - FVIII/Rag 173
  - GFAP 172, 173
  - immunohistochemistry 172–178
- glomus tumors 319, 478
  - GFAP 321
  - prognosis 321
  - S-100 321
- glutamine synthetase 61
- glycosaminoglycans (GAGs) 90, 92, 216
  - in experimental tumors 50–52
  - in meningiomas 354
- Gorlin's syndrome 26
- grading system 100, 103, 109, 215, 223
- granule cell tumors 335, 465
- growth of brain tumors 124–131, 169, 221
- growth fraction 113, 115, 120
- hamartoma 465–469
  - of the hypothalamus 465
- hemangioblastoma 402–411
  - cysts 409
  - GFAP-positive cells 405
  - in von Hippel-Lindau's syndrome 402
  - polycythemia 411
  - of spinal cord 402
  - Weibel-Palade bodies 404
- hemangiopericytoma 382–386
- hemorrhages in tumors 81
- hereditary hemorrhagic teleangiectasia 483
- hereditary tumor syndromes 475–483
- high linear energy transfer (LET)
  - radiation 512
- histogenetic classification of brain tumors 96–97
- homeobox genes 15, 16, 29
- Homer-Wright rosettes 278, 282, 291, 307
- honeycomb aspect 205, 216, 327
- human chorionic gonadotropin (HCG) 71, 419
- hydroxyapatite 91
- hypertermia 511
- immune response 92–95
- immunohistochemistry
  - of ependymoma 61, 66
  - of gliosarcoma 66, 69
  - of hemangioblastoma 61, 68
  - of medulloblastoma 61, 64, 65, 300–305
  - of medulloepithelioma 287
  - of melanoma 71

- immunohistochemistry
  - of neurinoma 58, 68
  - of neurocytoma 65
  - of neuroendocrine tumors 64, 65
  - of oligodendroglioma 58, 61, 63, 66
  - of paraganglioma 64
  - of pheochromocytoma 64
  - of pleomorphic xanthoastrocytoma 61
  - of plexuspapilloma 61
  - of subependymoma 61
- immunotherapy 519, 520
- incidence of CNS tumors 132, 133
- infantile desmoplastic ganglioglioma 267, 268
- insulin-like growth factor (IGF) 16, 17, 29
- intermediate zone 3
- invasiveness of brain tumors 124–131
- karyotypic analysis 113
- Ki-67 117–119, 120, 122, 185, 226
- laminin 66, 162, 183, 333, 488
- leptomeningeal fibroxanthoma 192
- leu-7 antigen 63, 65, 66, 223, 256, 268
- Li-Fraumeni syndrome 23, 333
- lipoma 462–464
- Lisch nodules 479
- loss of heterozygosity (LOH) 25, 26, 112
- Louis-Bar syndrome, *see* ataxia teleangiectasia
- Luse bodies 333
- lymphocytic infiltration 92–94
  - in astrocytoma 142
  - in glioblastoma 165, 187
  - in meningioma 367
  - in xanthoastrocytoma 192
- lymphomas 484–497
  - and AIDS 486, 493, 496
  - B cell 485, 491
  - chromosomal abnormalities 494, 495
  - classification 494
  - EBV 494, 496
  - epidural 496
  - immunoglobulins 490, 491
  - immunohistochemistry 488–491
  - incidence 486
  - neuroimaging 487
  - origin 493, 494
  - primary 484–497
  - secondary 485
  - survival 496, 497
  - T cell 485, 491
  - treatment 497
- lymphomatous leptomeningitis 485
- macrophages in gliomas 94, 142
- Maffucci's syndrome 397
- malignancy, concept 109–131
- malignant PNS tumors (MPNST) 333, 337, 339
- mantle zone 8, 10, 16
- marginal zone 3
- MDM2 oncogene 23, 115
- medulloblastoma 104, 289–307
  - in adults 307
  - apoptosis 291
  - calcifications 291
  - chemotherapy 305
  - congenital 289
  - cytogenesis 297–303
  - cytogenetics 299
  - desmoplastic 297
  - differentiation 299–305
  - DNA content 299
  - external granular layer (EGL) 300, 304
  - familial 289
  - incidence 289
  - melanotic 298
  - metastasis 305
  - pale islands 287, 300, 303
  - prognosis 305
  - radiotherapy 306
- medulloepithelioma 287
- medulloblastoma 298, 424
- melanoblastosis 388
- melatonin 275, 276, 284
- meningeal glioma 467
- meningeal gliomatosis 124, 169
- meningeal sarcomatosis 388
- meningioma 342–382
  - anaplasia 359–362
  - angiomatous 356
  - atypical 362
  - calcification 90, 369
  - chondroid 364
  - endotheliomatous 353
  - en plaque 353
  - fibroblastic 356
  - hormone receptors 375
  - hyaline degeneration 369
  - “iceberg” 352
  - infancy 343
  - in vitro culture 376
  - irradiation 344
  - lipoblastic 362
  - location 346
  - lympho-plasmacellular infiltrates 367
  - malignancy 359, 379, 380
  - melanin 364
  - metaplasia 362–367
  - microcystic 369
  - multiple 376, 478, 480
  - myxoid transformation 364
  - necrosis 367

- papillary variant 362
- proliferation 381, 382
- radiation induced 344, 345
- radiotherapy 382
- recurrence 380
- secretory 364
- sex prevalence 342
- trauma 344
- ultrastructure 374
- ventricular 347
- meningoangiomatosis 391, 480
- merlin 21
- metabolism of gliomas 185–187
- metastases 498–505
  - incidence 498
  - leptomeningeal 498, 500, 505
  - regressive events 502, 503
  - spinal 505
  - survival 503
  - treatment 503
- metastasis of brain tumors 122, 123, 189, 305
- methylnitrosourea (MNU) induced tumors 39–41, 51
- microhamartomas, glial 481
- microtubule associated protein (MAP)-2 268, 303–305
- molecular biology of brain tumors 18–29
- multicentric gliomas 126
- myelination 5, 7, 17
- N-myc 27
- necroses 80–83
  - with pseudopalisadings 80, 81, 179, 180
- neoplastic transformation 111
- nestin 7, 8
- neural cytogenesis 2–4
- neural differentiation 15, 16
- neural tube 1–3, 16
- neurinoma 322, 334, 477, 480
  - acoustic bilateral 323, 333
  - cellular 333
  - collagen 327
  - experimental 43
  - immunohistochemistry 333
  - intramedullary 325
  - malignant variant 336, 337
  - in vitro culture 333
  - in von Recklinghausen's disease 336
- neuroblastoma 308–313
  - cerebellar 303
  - differentiation 308
  - prognosis 311
- neurocytogenesis in post-natal life 110
- neurocytoma, central 268–270
- neurofibroma 319, 334, 335, 477, 479
  - diffuse 335
  - epithelioid variant 337
  - Pacinian 335
  - plexiform 335, 337, 477, 479
  - prognosis 336
  - in von Recklinghausen's disease 334, 337
- neurofibromatosis 477–482
  - NF1 20, 325, 477–480
  - NF2 21, 322, 323, 477, 478, 480, 481
- neurofibromin 20, 478
- neurofilaments 7, 64, 268, 303, 308
- neuronal markers 64–66
- neuron-specific enolase 64, 268, 275, 303
- neurothekeoma 336
- nude mice model of brain tumors 54
- O-2A cells 7, 17
- olfactory neuroblastoma 272–274
- oligoastrocytoma 221–223
- oligodendroglioma 214–227
  - anaplastic 223
  - astrocytes 221–223
  - calcifications 216–221
  - ENU-induced 216
  - immunohistochemistry 221–223
- Ollier's disease, *see* Maffucci's syndrome
- optic nerve glioma 198, 199, 478, 479
- osteomas 400
- osteosarcomas 401
- p53 22, 115, 121, 178
- paraganglia 319
- paraganglioma, *see* glomus tumors
- Parinaud's syndrome 276, 285
- perineurioma 336
- phenotypic heterogeneity 112
- pheochromocytoma 478
- photoradiation therapy 512
- photoreceptors 284
- physaliphorous cells 392
- pilocytic astrocytoma 142–147, 478
  - adult type 205, 206
  - in cerebellum 203–212
  - in cerebral hemispheres 142–147
  - juvenile type 205, 206
- piloprotoplasmic astrocytoma 146
- pineal cyst 285, 286
- pineal gland 275, 276, 319
- pinealoblastoma 281–285, 315
  - differentiation 284
  - melanotic deposits 285
  - prognosis 285
- pineocytes 275
- pineocytoma 277–281, 285
  - differentiation 278
  - prognosis 281
- placental alkaline phosphatase (PLAP) 419
- platelet-derived growth factor (PDGF) 7, 17, 28, 182, 183



- platelet-derived growth factor (PDGF)  
   in glioblastoma 165  
   receptors 28
- pleomorphic xanthoastrocytoma 190–193
- plexus carcinoma 259
- plexus papilloma 254–259  
   malignant variant 259
- polar spongioblastoma 311–313  
   step-ladder aspect 313
- prickle cells 448
- primitive neuroectodermal tumors (PNET)  
   55, 104, 105, 289
- prognosis  
   of anaplastic astrocytoma 151  
   of astrocytomas 150–155  
   of cerebellar astrocytoma 210–212  
   of glioblastoma 185–187  
   of gliosarcoma 178  
   of glomus tumors 321  
   of medulloblastoma 305–307  
   of neuroblastoma 311  
   of oligodendroglioma 226  
   of pilocytic astrocytoma 154, 155  
   of xanthoastrocytoma 193
- proliferating cell nuclear antigen (PCNA)  
   115, 119, 120, 130, 304
- prostate-specific antigen (PSA) 71
- psammoma bodies 356, 369–374
- pseudocalcium 90, 217
- pseudopsammoma bodies 366
- pseudoxanthomatous cells 405
- Purkinjoma 266
- radial glia 4, 8, 11–14
- radionecrosis 188
- radioprotectors 512, 513
- radiosensitizers 510, 511
- radiotherapy 504–511  
   accelerated fractionation 509  
   of anaplastic astrocytoma 155  
   associated with chemotherapeutic agents 508  
   of astrocytoma 151  
   biological basis 506–513  
   of cerebellar astrocytoma 210  
   of craniopharyngioma 458  
   dementia after 528  
   effects on human brain 523–530  
   effects on human brain tumors 522, 523  
   effects on human spinal cord 531, 532  
   of ependymoma 249  
   of glioblastoma 188  
   hyperfractionation 509  
   of lymphoma 497  
   of medulloblastoma 306  
   of metastases 503  
   neuropsychologic deficits after 528  
   of oligodendroglioma 226, 227  
   pathogenesis of adverse effects 532, 533
- ras 115, 121
- Rathke's fissure (clef) cysts 436, 454, 458
- RB1 gene 18, 19, 315
- regressive events in tumors 80–83
- resorptive carcinogens 39, 40
- reticulin 488
- reticulum cell sarcoma 484
- retina, tumors 313–318
- retinal angiomas 481, 483
- retinoblastoma 19, 285, 315–318  
   differentiation 315  
   immunohistochemistry 318  
   trilateral 19, 285, 315
- rhabdoid tumors 429
- rhabdomyosarcoma 427–429
- risk factors for brain tumors 30  
   AIDS 33  
   alcohol 36  
   barbiturates 31  
   contraceptives 31, 36  
   N. nitroso compounds 32, 35–37  
   non ionizing radiation 36  
   phenytoin 31  
   radiotherapy 34  
   second tumors 35  
   tobacco smoking 31, 35  
   trauma 33
- Rosenthal's fibres 79, 137, 146, 196–198, 200, 202, 206, 209, 211, 213, 285
- S-100 58, 333, 336, 337
- S-retinal antigen 276, 284, 304, 318
- sarcoglioma 178
- satellitosis 216
- Schwannoma, *see* neurinoma
- schwannosis, intramedullary 478, 479
- spongioblastoma 137, 138, 198, 204
- stem cells 2, 9
- Sturge-Weber's disease 90, 221, 482, 483
- subependymal giant cell astrocytoma 193–196, 475
- subependymal glia 137
- subependymoma 249–251
- subependymal layer 8, 9
- SV 40 large T antigen 19, 55, 305
- synapsin I 303
- synaptophysin 65, 268, 303
- tanocytes 14, 197
- tau protein 304, 305
- teratocarcinoma 419
- teratoma 419
- transforming growth factor (TGF)- $\beta$ 1 29, 131, 169, 184

- transgenic mice 23
- transthyretin 256
- trilateral retinoblastoma 285, 315
- triton tumor 337, 479
- tuberous sclerosis 475–477, 481
- tumors of the spinal cord
  - astrocytomas 213
  - epidemiology 136
- tumor suppressor genes 475, 482
- Turcot's syndrome 24
  
- vascular endothelial growth factor (VEGF)
  - 184, 185
- vascular malformations 468–474
  - arteriovenous 472
  - capillary teleangectasia 469
  - cavernous angiomas 46
- ventricular zone 2, 6
- vessel markers 66, 67
- vimentin 12, 60, 68
  - in pilocytic astrocytoma 146, 205
  - in reactive astrocytes 74, 76, 78
  - in xanthoastrocytoma 192
- viral carcinogenesis 51, 52
- Von Hippel-Lindau's syndrome 481, 482
- Von Recklinghausen's disease, *see* neurofibromatosis
  
- Weibel-Palade bodies 66, 179
- Wyburn-Mason syndrome 483

# Springer and the environment

At Springer we firmly believe that an international science publisher has a special obligation to the environment, and our corporate policies consistently reflect this conviction.

We also expect our business partners – paper mills, printers, packaging manufacturers, etc. – to commit themselves to using materials and production processes that do not harm the environment. The paper in this book is made from low- or no-chlorine pulp and is acid free, in conformance with international standards for paper permanency.



Springer